ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 52 SEPTEMBER 1959 FASC. 3

SACROCOCCYGEAL AND VERTEBRAL CHORDOMAS AND THEIR TREATMENT

by

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A chordoma is one of the most difficult tumours to treat. Not a single one of the some 200 chordoma cases reported may be said definitely to have been permanently cured although the prolonged course, with years of freedom from symptoms after different forms of treatment, has in some instances suggested a hopeful outcome.

Endeavours have been made during recent years to devise a more consistent form of therapy based on an improved knowledge of the characteristics of the tumour. Chordomas are believed to arise from remnants of the notochord. They may occur at the base of the skull and along the entire length of the vertebral column, the most common site being the sacrum and coccyx where approximately one half of all chordomas are situated. Those occurring at the base of the skull come next in order of frequency (circa 40 %) while chordomas in the vertebrae proper are relatively rare.

The possibility of radical surgical therapy is almost non-existent in the case of the tumours at the base of the skull and in the cervical, thoracic and lumbar vertebrae. Chordomas in the sacrococcygeal area are theoretically more accessible to operative treatment, and in recent

Submitted for publication 17 March 1959.

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years interest has mainly been concentrated on devising a suitable surgical approach to this region. Although most workers recommend as complete surgical removal as possible, a few consider that repeated local excisions are likely to give good palliative results.

Chordomas are considered to be fairly resistant to radiation therapy, and until recently the possibility of achieving any curative effect with this form of treatment has not been viewed as hopeful; opinions have varied, on the other hand, regarding its use for palliative purposes.

Material

Our material of histologically proven chordoma consisted of 16 cases, all except one of which (Case 16) had received treatment at Radiumhemmet. In the majority of the surgically treated cases the operation had been performed at Karolinska Sjukhuset.

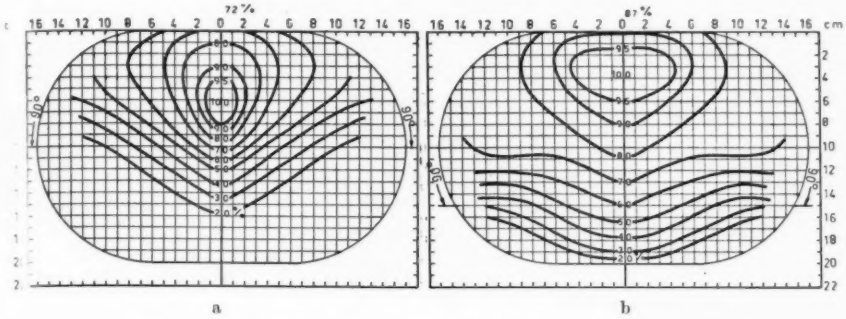
Of the 16 patients, 9 were men, one of them a child, and 7 were women. Most of the patients were in the 50 to 70 years age-group. The material, however, contained 1 patient aged 4 years, 2 between 20 and 40 years of age, and 1 aged 75. Thirteen of the chordomas were in the sacrococcygeal region, 2 had originated in a lumbar vertebra, and 1 in a thoracic vertebra.

Case reports

Case 1. Male, aged 67, who had received an injury to the sacral region 7 years previously, complained of pain and swelling of 6 months' duration over this region. A chordoma was diagnosed after punch biopsy at the end of December 1937. On admission, a tumour, twice the size of a fist, located mainly ventral to the sacrum was palpated.

Roentgen treatment was commenced in the middle of January over 7 fields, 2 dorsal fields receiving 2 800 r each and 2 ventral fields 2 400 r. In addition a dose of 1 000 r was applied to 1 perineal field and 1 200 r to 1 lateral field on each side, and a depth dose of about 3 000 r over 28 days was given to the centre of the tumour. (For details of treatment see p. 188.) In March the pain disappeared and regression of the tumour was established by palpation; in April there was evidence of further regression. In May no tumour could be palpated dorsally over the sacrum and examination per rectum disclosed only a small transverse, banana-sized swelling. When seen in September 1939, and again in July 1940, the patient had no pain; the signs, however, were unchanged. He had a recurrence in November, and death occurred in February 1942.

Case 2. Male, aged 51, with a history of trauma to the lumbar spine 6 years previously, had suffered for 5 years from low backache with pain radiating down both legs. A second injury to the same region had occurred one year before. At operation performed at an orthopaedic clinic in May 1955 for possible prolapsed intervertebral disk suggested by myelography, a small tumour partly growing into the body of L3 was found. The operation was not definitely radical.



a b

(Courtesy: Dahl & Vikterlöf: Acta radiol. (1958) Suppl. No. 171.)

Diagram 1. Dose distribution in arc therapy. Tube voltage 200 kV constant, filter 0.5 mm Cu + 1 mm Al, HVL 1.1 mm Cu. FSD 50 cm. 180° rotation. a) Case 2. Surface field area 4 × 10 cm, centering depth 10.0 cm. b) Case 14. Surface field area 6 × 10 cm, centering depth 15.0 cm.

The growth proved to be a chordoma and roentgen therapy was instituted, 2 500 r being applied to one dorsal field over the lumbar spine over a period of five days. The patient was almost free from pain for a short time but about 2 months later the pain down the legs returned. In January 1956 the signs were unchanged but the patient was feeling better, with little discomfort attributable to the tumour, and again in December he still had no pain. In October 1957 the pain in his left leg had increased, and roentgenography revealed a recurrence in the body of L4.

Roentgen arc therapy was commenced, a tumour dose of 2 600 r being given over 16 days. (Cf. Diagram 1a.) In January 1958 the patient felt better but in February he was worse again and roentgenography showed unaltered appearances. Arc therapy was then again instituted, a tumour dose of 750 r being delivered in 5 days. This was followed by telegamma arc treatment (Radiumhemmet's gammatron charged with 1 000 curies of cobalt-60), with pendulation on 2 lateral fields with a tumour dose of 2 255 r in 19 days. The fields were opposed and a pendulation angle of 40° was used; the surface field area was 6 × 11 cm, the FSD 50 cm and the centering depth 9 cm. When the patient was seen in April 1958 it was found that his condition had undergone further deterioration.

Case 3. Male, aged 37, had sustained injury to the sacrum 3 times, on the last occasion in 1943, and for the previous 18 months had had pain in the small of his back, extending down the legs during the previous year. Defaecation difficulties had been experienced in the past month. On admission, no outward signs of tumour were apparent, but rectal examination disclosed a large mass, the upper border of which could not be palpated.

Roentgen examination revealed a large area of destruction in the sacrum; the greater part of S3 as well as the vertebrae below were destroyed but S1 and S2 were normal in appearance.

Roentgen therapy was given at the end of 1947, 2 000 r per field being applied to 2 dorsal and 2 ventral fields. The depth dose was 2 400 r delivered to the centre of the tumour in 26 days. Slight regression was noted in February. The patient received additional roentgen treatment for 14 days in April with 1 200 r to each of the 4 previously

treated fields; a dose of 1 400 r was delivered to the tumour centre during this period. He felt much better in June and in November 1949 the tumour showed considerable regression. In June 1951 the patient had no pain and the upper margin of the tumour could now be reached with the finger. Localized pain had returned in May 1953 and in April 1954 the pain had increased and both palpation and roentgenography showed progression of the tumour, although there were still no roentgenographic changes in S2. An operation was performed to remove the tumour, resection being performed through the middle of S2. It was considered that all traces of the tumour had been removed, but histologic examination revealed streaks of tumour cells right out into the operative surface. The growth was a chordoma. In March 1956 the patient had no pain and there were no signs of recurrence. Roentgenography in October revealed a recurrence; in May 1958 this was palpable but the patient remained symptom-free.

Case 4. Boy, aged 4 years, in whom over a period of 18 months a tumour had developed over the right side of the sacrum. When admitted he had a tumour slightly larger than a mandarine which bulged towards the true pelvis. Biopsy was performed in May 1954 and a chordoma diagnosed.

Roentgen treatment was inaugurated at the end of June to 1 dorsal field but was discontinued after 500 r had been given. The tumour was removed as completely as possible but the excision was not radical, some of the tumour tissue in the lateral area being left in situ in order to avoid damage to the nerves. Sacral resection at the level of S2 was performed. A postoperative dose of 900 r was given to 1 dorsal field. Local recurrence was evident under the cicatrix, and in October a chordoma in the soft tissue in the old operative field was removed. Postoperative roentgen treatment of 1 400 r to 1 dorsal field was administered over 5 days. Recurrence was thought to be likely in January 1955 and confirmed in March, when glandular metastases in the groins were also established. The patient when seen in September was in poor condition; he had paresis of the bladder and paralysis of both legs. Death occurred in August of the following year. Metastases in the vertebral bodies, lungs, and right adrenal gland, as well as in numerous regional and intra-abdominal lymph nodes, were found at autopsy. There was also a large local recurrence. The histologic appearances were typical of malignancy and essentially the same as at operation and biopsy in 1954.

Case 5. Female, aged 58, received an injury to the lumbar spine in 1936 with subsequent aching pain in the small of the back and down the right leg. Bone destruction in L4 was roentgenographically established in 1947.

The patient had received roentgen treatment at another hospital in accordance with the following dosage scheme: 750 r in May 1947, 800 r in July 1947, 600 r in September 1947, 600 r in October 1950, and 800 r in October 1953. All these treatments had been applied to 1 dorsal field and had at first produced good palliative results with almost complete freedom from pain. The last two series had had no effect, however. In January 1954 roentgen examination revealed that L4 was compressed to about 1 cm in height; all the soft-tissue tumour was removed in February but the destroyed vertebra was not touched. Roentgen treatment was given in April, each of 2 dorsal fields over the tumour area receiving 1 800 r. When seen a year later the patient was slightly disabled but the tumour had not progressed. The condition was unchanged in May 1958.

Case 6. Female, aged 48, with no history of trauma. A few months after partus in 1941 she noticed a small bulge over the coccyx. On admission in February 1950 a rounded tumour about 10 cm in diameter was palpated. Roentgen examination revealed destruction of the coccyx, only C1 being intact. All traces of a soft-tissue tumour were excised in May but histologic examination proved that the intervention had not been radical; the tumour was a chordoma.

Postoperative roentgen treatment over a period of 5 days was given, 2 500 r being applied to 1 dorsal field over the tumour area. Examination in March 1951 disclosed a recurrence; the bone destruction had not increased in extent but a soft-tissue tumour had redeveloped. A month later the sacrum was resected between S4 and S5 and the entire tumour area was excised. Surrounding macroscopically sound tissue was included in the excision but microscopy indicated that the operation had not been completely radical. In April 1953 the patient had no pain and there was no obvious recurrence. She reported by letter in April 1955 and again in December 1957 that she was free from discomfort.

Case 7. Female, aged 58, had received an injury to the sacrum in 1930, after which she had had pain in the small of the back and in January 1938 noticed a bulge over the right side of the sacrum. When seen in July she had a tumour as large as an orange bulging in towards the rectum; a chordoma was diagnosed by punch biopsy.

From July to August a roentgen dose of 2 800 r was applied to each of 2 dorsal fields and 2 400 r to 2 ventral fields. A dose of about 2 800 r over 29 days was delivered to the centre of the tumour. All symptoms disappeared. In November she received another injury, followed by the same pain as before, and additional treatment of 1 200 r per field was applied to the previously treated fields. The clinical findings remained consistently unchanged. She returned home and died about three weeks later.

Case 8. Male, aged 66, with no history of trauma, had felt occasional pain in the sacral region since 1920; this became suddenly worse in February 1939. On admission in 1939 he was found to have a tumour the size of an orange protruding both dorsally and inwards towards the rectum.

Roentgen treatment was given for four weeks in March and April; 3 dorsal fields received 2 000 r + 2 000 r + 1 500 r and 3 ventral fields 2 000 r each. A dose of about 4 000 r over 29 days was delivered to the tumour centre. At the conclusion of the treatment the patient had no symptoms. Punch biopsy gave a diagnosis of chordoma. Repeated follow-ups showed that the tumour was gradually decreasing in size. In May 1940 a plum-sized tumour was palpated. The patient was still without pain. The condition was unchanged in August 1944, but in the middle of October the tumour had grown to the size of an orange, and the prostate was exceptionally firm. Roentgen therapy was given in November, 1 000 r being applied to each of the 6 fields previously treated and a dose of about 2 000 r delivered to the tumour centre over a period of 16 days. The condition was unchanged in June 1945. In November the patient was in considerable pain and mentally confused. Death occurred in January 1946 but no details are available.

Case 9. Female, aged 75, had received an injury to the sacrum many years previously. Early in 1939 she began to feel pain in the sacral region, noticed a lump over the sacrum, and had pain on defaecation. When admitted in January 1940 she had a tumour probably about 15 × 15 × 10 cm in size. On roentgen examination there was evidence of destruction of the entire coccyx but the sacrum appeared to be intact. Punch biopsy disclosed a chordoma.

Roentgen treatment consisting of 2 000 r per field was applied to 2 dorsal and 1 perineal field, and 1 600 r per field to 2 ventral fields, the dose to the centre of the tumour being 3 500 r over 26 days. The tumour had decreased to about half its original size in April. Both the dorsal fields now received 300 r spread over 2 days and a week later all obvious traces of the tumour were excised and the sacrum resected between S4 and S5; it was doubtful, however, whether the intervention had been radical. Up to March 1941 the patient had no pain and there were no signs of recurrence, but in June she had sacral pain although no abnormal signs were present. In January 1942 she had backache and

roentgen examination disclosed bone destruction in Th8 and Th10. In March scattered accumulations of glands in the pelvis suggested metastases although no microscopic confirmation was obtained; the gland metastases had progressed by April and glands had also appeared in the right groin. In September she had a transverse spinal lesion with paralysis of both legs. Death occurred in February 1943. No autopsy was performed.

Case 10. Male, aged 57, with no history of trauma, for a few years had had occasional pain in the right leg. At operation in January 1927 a sacral chordoma was shelled out but it was obvious that tumour tissue had been left in the walls of the cavity. Radium tubes were implanted.

Postoperative roentgen therapy was given in February. The dosage given is now difficult to judge; probably, about 1 000 r were applied to 2 dorsal fields over a period of 21 days. In August the patient had no symptoms and there were no signs of recurrence. He received about 1 000 r to each dorsal field over 4 days in January 1928; no symptoms or signs present. A dose of about 1 500 r was applied to 1 large dorsal field over 9 days in August and about 1 300 r to the same field in October. There is no record of the patient's response to these treatments. A recurrence was evident in October 1930 and in November a dose of about 1 200 r was delivered to 2 dorsal fields over 5 days. Implantation of radium tubes was performed in the beginning of December. Death occurred in January 1931. No autopsy was performed.

Case 11. Female, aged 27, with a year's history of dorsolumbar pain. At operation in August 1940 a chordoma infiltrating the muscles on the left side of Th6 to L2 was electrocoagulated but the vertebrae were not touched. The patient was admitted in October and received 2 900 r to 1 field in the operative area over 10 days. There were probable metastases in the left axilla. Death occurred in November. No autopsy was performed.

Case 12. Female, aged 58, with no history of injury, had noticed a tumour over the sacrum in 1935 and experienced occasional dull pain. At first the tumour had varied in size, but since the autumn of 1937 it had grown larger and caused pain on defaecation and, from the spring of 1938, weakness of the left leg and vesical tenesmus. On admission in August the tumour was the size of a fist; the part dorsal to the sacrum covered an area of 12 × 14 cm and appeared to be lobulated into two masses separated by an indentation. A chordoma was established by punch biopsy.

Two dorsal fields and 1 lateral field on each side of the sacrum each received 2 000 r; a dose of about 3 300 r was delivered to the centre of the tumour over 32 days. Considerable regression of the tumour was evident in January 1939, the tumour dorsal to the sacrum then measuring 7 × 10 cm; the patient had no pain. Further therapy was inaugurated; the previous 4 dorsal fields were combined into 2 and these 2 fields each received 800 r, the 2 ventral fields each receiving 2 000 r. In September the condition was unchanged. Sacral pain had returned in April 1940 and a roentgen dose of 800 r per field was applied to the 4 original dorsal fields and to the 2 lateral fields over 14 days. The patient felt considerably better for a short period after this treatment. Palpation revealed no change in September but the patient complained of severe sacral pain, this being unaffected by the administration of 800 r to the lateral and 400 r to the ventral fields over 7 days. The tumour was still growing larger in January 1941; further therapy consisting of 900 r to each of the 2 dorsal fields and 600 r to the 2 lateral fields had no palliative effect. Death occurred in May 1942. No autopsy was performed.

Case 13. Male, aged 68, with no history of injury, had had pain in both hips, considered to be due to marked arthrosis deformans, as well as constipation, for 12 years. On admission in February 1935 a mandarine-sized tumour adherent to the sacrum was palpated per rectum; no other changes. A chordoma was established by punch biopsy.

The treatment administered consisted of 1 500 r to 2 dorsal and 1 ventral fields and 1 400 r to 1 lateral field on the left side, giving a dose of about 2 400 r in 21 days to the centre of the tumour. There was slow improvement in response to this treatment, and in December 1936 the tumour seemed to have decreased and the patient had little pain; he was again given roentgen treatment, one of the dorsal fields receiving 1 750 r and the other 1 500 r; each of 2 ventral fields received 1 750 r, the depth dose being about 2 200 r in 3 days to the tumour centre. The tumour showed continued regression and the patient was asymptomatic in March 1937 when a further dose of 1 000 r was applied to 1 perineal field and an additional dose of 250 r to the previous ventral and dorsal fields. The patient had no symptoms till September 1939, when sacral pain again occurred. There was no change in the condition on palpation in October when 1 200 r was applied to the perineal field and 900 r to the previous 2 ventral and 2 dorsal fields and to the lateral field over 21 days. The pain subsided; it reoccurred in July 1940 and death took place a year later. No autopsy was performed.

Case 14. Male, aged 64, received an injury to the sacrum in May 1951 and shortly afterwards a walnut-sized tumour ventral to the lower end of the sacrum and adherent to the bone was discovered; no treatment was given. The condition was unchanged in September 1953 and roentgen examination disclosed destruction of the entire coccyx as well as S5 and parts of S4. The sacrum was resected between S4 and S3; the intervention appeared to be radical. The patient was asymptomatic till May 1955, when he complained of sacral pain and slight difficulty in micturition. Roentgen examination now revealed progression, with partial destruction of S3. Resection of the sacrum between S3 and S2 was performed in July and a diagnosis of chordoma confirmed. Microscopy showed that radical resection had not been achieved.

Postoperative roentgen treatment with 2 400 r to 2 dorsal fields was administered over 12 days. No abnormal signs or symptoms present in January 1956. In August, however, there was roentgen evidence of a recurrence and a mass was palpated on the inner aspect of the sacrum.

Roentgen arc therapy, consisting of a tumour dose of 2 550 r in 20 days (cf. Diagram 1b) was then administered. All pain disappeared and in January there was no evidence of abnormality on palpation. A recurrence was again established by roentgen examination in November and the patient had incontinence and difficulties in walking. Telegamma arc therapy (1 000 curies of cobalt-60) was administered over 16 days to 2 lateral fields, with a tumour dose of 1 850 r; the surface field area was 10 × 16 cm and the FSD 70 cm. The patient's symptoms abated rapidly and his condition was unchanged when he was last seen in May 1958.

Case 15. Female, aged 58, with no history of injury, had since 1943 noticed a slow-growing lump over the coccyx, and there had been tenderness in the sacral region since the spring of 1948. On admission in December a tumour about the size of a fist, projecting both dorsally and ventrally from the coccyx, was observed; its greatest diameter was estimated to be about 12 cm. Roentgen examination disclosed coccygeal destruction with the uppermost vertebra apparently intact. Resection of the sacrum between S3 and S4 was performed, the excision being apparently radical. A diagnosis of chordoma was established and it was also confirmed that the tumour seemed to have been completely removed. No roentgen therapy was given. The patient had no return of symptoms but died of carcinoma of the uterus six years later. No autopsy was performed.

Case 16. Male, aged 51, injured the coccyx in 1950 and since 1952 had had aching pain in the small of the back. He was admitted to a country hospital in 1954, where a sacral tumour was diagnosed.

Roentgen treatment was administered to 2 fields over the sacrum on several occasions; the data are in some respects difficult to interpret, but in no series of treatments had tumour doses of the size aimed at in the other cases in this material been employed. The final dose, however, was so large that extensive ulceration had occurred in the sacral region. The patient's symptoms were not noticeably affected, and he was admitted to this surgical clinic in May 1956. At that time he had disabling sacral pain and a sacrococcygeal tumour the size of a child's head which had destroyed the sacrum below S2. Resection of the sacrum and coccyx through S2 was performed. As much of the soft-tissue component of the tumour as possible was excised, but it was realized that the intervention had not been radical. A diagnosis of chordoma was established. Comprehensive plastic surgical measures were required to cover the skin defects resulting from the radiation treatment. The symptoms abated rapidly and had practically disappeared by October. A report from the local hospital at the end of 1957 stated that the patient had a recurrence with moderately severe symptoms.

Clinical aspects

A few authors consider that trauma may have some significance in this condition through a release of notochordal tissue. Trauma was mentioned in the history of 7 cases in our material. As injuries, especially to the sacral region, are a common occurrence and as the time between the supposed injury and the diagnosis amounted to several years in most of the cases, it is not possible to assess the influence of trauma with any certainty.

The length of the case histories in our material varied between 6 months and 15 years, counted up to the time of the patient's admission to our hospital. The most common initial symptom (9 cases) was localized aching pain, combined in 3 cases with pain radiating down the legs, the latter probably being a result of nerve compression. In 2 cases the pain set in at about the time a tumour was discovered and in 5 cases a tumour was observed before the onset of pain. In one case the history of the chordoma could not be satisfactorily interpreted because of the presence of other diseases.

As soon as a sacral chordoma has expanded dorsal to the sacrum it is fairly readily diagnosed. Some chordomas, however, spread mainly inwards in the pelvis and in these, digital examination of the rectum is of decisive diagnostic significance. Our material contains patients who, despite long-standing local sacral pain, some even with defaecation difficulties, had not been examined per rectum.

Considering the genesis of the chordomas, it is natural that they should be situated in the median line or close to it. They appear in the roentgenograms as osteolytic bone lesions without specific characteristics (Utne & Pugh, Lindbom). No calcifications are observed in vertebral and sacrococcygeal chordomas but scattered remains of bone may be visible for a long time. The extent of the intrapelvic soft-tissue compo-

nent may be assessed to best advantage in roentgenograms taken with a contrast-filled rectum.

The patient's symptoms and the clinical and roentgenologic signs may direct attention to the possibility of chordoma. These are of no value, of course, when a chordoma is to be distinguished from some other solitary osteolytic bone lesion in the same situation. We have, for example, encountered cases in which it was both clinically and roentgenologically impossible to make an accurate differential diagnosis between a chordoma and a giant-cell tumour.

A correct diagnosis can be established only by histologic examination. There has been some discussion as to the advisability of performing biopsy in malignant bone tumours, because of the risk of spread. Nine of our 10 patients were operated upon without preliminary biopsy. In one of the patients subjected to operation and in all those not treated surgically punch biopsy was performed. In our opinion, a diagnosis of chordoma should always be confirmed histologically before any treatment is instituted. It is only after this has been done that an adequate plan of action for the operation can be set up, and only then can radiation therapy be arranged to give the best effect. The risk of spread is so small with this type of tumour that the advantages of well-planned therapeutic treatment outweigh the risks.

Chordomas do not often form metastases; according to the literature the figure is 10 % of all cases. Metastases were clinically established in our material in 3 cases. In only one case, however, was histologic confirmation obtained. All three cases had metastases in adjacent regional lymph nodes but in the case with histologically confirmed metastases new foci were also present in the lungs, skeleton, and one adrenal gland. These 3 cases had previously been treated surgically.

Pathology

Chordomas are composed of characteristic large cells with vacuolated cytoplasm. The nuclear polymorphism is moderate and mitotic figures are not often present. These histologic appearances have long been recognized. Some investigators also state that the tumours are encapsulated in a layer of connective tissue. The tumour tissue is criss-crossed with strands of connective tissue having the same structure as the enveloping capsule and the tumour is consequently lobulated. The mode of growth is said to be mainly expansive, at least as regards the soft parts.

The cellular structure of the chordomas in our material was in all essentials the same as has been described by other workers. In 5 of these cases the histologic diagnosis was made from material obtained only

by punch biopsy and it was obviously not possible to form any opinion regarding the periphery of the tumour. In the 11 cases in which the tumour was excised, however, we studied this area as thoroughly as possible with a view to obtaining information on the mode of growth.

In the 7 cases in which the periphery of the chordoma could be studied a capsule-like band of connective tissue separated the tumour from other soft tissue. In all of them, however, small groups of tumour cells were present in this connective tissue. In every case tumour tissue was also found outside the capsular band of connective tissue, in the muscle tissue, subcutis or other surrounding tissue. A similar observation was mentioned in 1955 by SHACKELFORD & ROHDE, who wrote: 'in some instances, at least, the capsule is invaded by tumor cells'.

In none of the tumours was any connective tissue layer observed between the tumour and the bone: the tumour tissue lay directly against the bone. The tumours were obviously growing into the marrow spaces of the bone by infiltration, and tumour infiltration was established far beyond the roentgenologically demonstrable areas of destruction.

The histologic findings revealed that in 6 of the 7 tumours removed by operation the intervention had not been radical, although in several instances it was considered that all traces of the growth had been satisfactorily removed. From the histologic evidence regarding the peripheries of the tumours it may be concluded that radical excision cannot be achieved by shelling out the tumour along its capsular boundaries.

Surgery

It is perhaps remarkable that it has not been possible to remove accessible chordomas in the sacrococcygeal region radically enough to achieve a complete cure. One of the contributory causes of this is undoubtedly that the slow-growing nature of these tumours has made it difficult to compare the effects of different operative techniques. LITTMAN has described cases in which repeated local excisions or excochleations without any attempt to achieve a radical result have given freedom from pain for several years.

Chordomas seldom form metastases through the blood or lymph streams. Most of the deaths are caused by local recurrence in the sacrum with propagation mainly in towards the pelvis. This certainly suggests that endeavours to carry out more radical primary interventions must be intensified. A more radical operative technique has already been worked out by MACCARTY, WAUGH, MAYO & COVENTRY, and by SHACKELFORD & ROHDE.

The experiences of these investigators as well as our own observations indicate that a broad area outside the capsule should be included in the

ex ision. The separation of the rectum, which is never involved in the tu our, has not caused either the aforementioned authors or ourselves an difficulty.

With regard to the intraosseous portion of the tumour these surgeons str ss the following features: First, the intraosseous tumour presumably oft n propagates along the path of least resistance, in other words within the sacral canal. This feature has been demonstrated by SHACKELFORD & RO DE. Secondly, both the S2 nerve roots as well as the S3 root on one side mu t be preserved if normal bladder function is to be retained. Both these fea ures necessitate the performance of laminectomy. It is then possible to etermine the uppermost extension of the tumour within the sacral can l fairly accurately, and at the same time the roots of the second and thi l sacral nerves can be dissected free and preserved even if the whole of the third, and parts of the second, sacral vertebra must be sacrificed. The retention of S1 seems to be all that is necessary to ensure pelvic stability. The entire tumour should, if possible, be removed in one mass.

Only one operation of this type has been performed at Karolinska Sjukhuset, with the assistance of a neurosurgeon; this was in a case of an advanced chordoma (Case 16) given only radiation therapy for 5 years and previously diagnosed as inoperable. A good palliative effect was obtained but 18 months after the intervention the patient had a large local recurrence with areas of destruction in S1 and the iliac wing on one side.

A further 10 cases in our material received surgical therapy. In 5 of these, including all the chordomas in the thoracic and lumbar spine, it was appreciated that the intervention was not even grossly radical. In the others, the resection was made in tissue both roentgenologically and macroscopically normal; yet histologic examination revealed tumour tissue in the excision surface in 4 cases. In these cases resection of the sacrum was carried out to a distance corresponding to the height of a half to one and a half vertebral bodies above the border of the roentgenologically demonstrable destruction. In spite of this, roentgen examination in all the recurrences showed continued destruction in the remaining portions of the sacrum.

In only one case does the operation seem to have been radical in as much as no tumour tissue was demonstrated in the excision surface. The chordoma was the size of a fist but at the time of observation in hospital it had destroyed the coccyx only below the first coccygeal vertebra. The sacrum was resected between S3 and S4, in other words, so as to leave a gap of three vertebrae between the area of resection and the destroyed bone. The patient had no subsequent discomfort over a period of 6 years until she died of carcinoma of the uterus.

Our experiences suggest that resection of the sacrum has little hope

of being radical unless it is possible to include in the excision tissue t a height corresponding to at least two vertebral bodies above the up er margin of the destruction visible in the roentgenogram.

Radiotherapy

In several of the papers published in recent years radiation treatm nt has been considered capable of producing a palliative effect. Pain as been eliminated and in some instances considerable regression of he tumour has been observed (DAHLIN & MACCARTY, FRIEDMAN, Woo D). Several investigators have stressed the importance of giving as la ge roentgen doses as possible. MONTGOMERY & WOLMAN and WOOD h ve considered it likely that chordomas in children have greater radiosensitivity than chordomas in adults.

During the past few years the first results from supervoltage therapy have been published, and information regarding two chordoma cases treated by this method is now available. BAKER & COLEY treated a chordoma in a lumbar vertebra with a tumour dose of 4000 r in less than 30 days. They used the one million volt technique, applying treatment over three fields. 'Primary healing' of the chordoma was achieved. FRIEDMAN gave another chordoma in a lumbar vertebra two million volt therapy with the rotation technique, delivering a tumour dose of 7200 r in 47 days. The defect in the bone healed and the symptoms disappeared. At the time of writing the observation time is 4 years.

The value of combined surgical and roentgen treatment has received little attention, and very few cases have been studied. KEY & BERVEN stressed the importance of postoperative radiation therapy, at least in those cases in which the operation has not been radical. These authors also discussed the possibility of pre-operative roentgen treatment. SANDAHL and FLETCHER, WOLTMAN & ADSON also recommended combined treatment.

All except one of our patients received roentgen therapy. The treatment data in the different cases showed much variation, however. Chordoma is such a rare disease, and the treatment results have hitherto been so variable, that no definite rules for radiation therapy in this form of tumour have as yet been evolved. A certain amount of variation in the treatment scheme can obviously never be entirely avoided, because of the variations in the size and location of the tumours.

Some of the treatment data were fairly consistently applied. In most cases, for example, a voltage of 170 kV, an FSD of 50 cm and a filter of 0.5 Cu + 1 mm Al were employed; a special tin filter (Thoraeus filter) was, however, used in a few cases. The half-value layer was 0.9 mm Cu when treatment was given with a Cu-Al filter and 1.6 mm Cu with

a n filter. The amperage varied. Before 1938, 6 mA was used, from 1938 to 940, 7 mA, from 1940 to 1954, 15 mA, and from 1954 onwards 20 mA. Tl dose rate was influenced by the variations in amperage. Up to 1954 th rate was 40 to 45 r per minute with an FSD of 50 cm. For the past tw years the rate has been 90 to 100 r per minute at the same distance.

All doses were measured on the skin and thus included back-scatter. In he planning of the treatment fields, endeavours were made to achieve as omogeneous a tumour dose as possible. The size and position of the fie ls were therefore chosen so that the entire tumour, or as much of it as ossible, would be irradiated each time treatment was applied. The fie ls varied in size from 100 to 250 cm². Therapy was given each day to ne field and the daily dose varied between 300 and 500 r, depending on he size of the field. The usual dose was 400 r. The one child in our ma erial formed an exception; apart from a few doses of 300 r he received dai y doses of 100 and 200 r. The final doses per field in each treatment seri s will be found in the case histories; they generally amounted to 2500 to 3200 r.

An attempt has been made to calculate the doses at the centre of the tumour for some of the larger treatment series. In the absence of exact measurements these depth doses must be regarded as approximate and maximum values. These figures will also be found in the case histories.

Two patients (Cases 2 and 14) have received treatment during the past year both in the form of roentgen arc therapy, and of telegamma arc therapy with the gammatron at Radiumhemmet charged with 1 000 curies of cobalt-60. The treatment data and dose distribution used in the former will be seen from Diagram 1 (DAHL & VIKTERLÖF). The data for the gammatron treatment (HULTBERG et coll.) will be found in the case histories. In both instances these treatments were additional measures given for purely palliative purposes to previously irradiated patients. These forms of treatment have not yet been fully developed and our reports are consequently only of limited value in this respect.

Our experiences in this small, heterogeneous series of chordoma cases are obviously only a small contribution to the problem of deciding upon satisfactory general principles for radiation treatment in this condition. Certain observations were so typical, however, that, together with a knowledge of the general course of the disease and the findings regarding the pathology of the tumours, they might be used as a basis for a discussion of the guiding principles in the treatment.

We were able to study the effect of radiotherapy alone in 7 patients. The other patients received roentgen treatment mainly as a postoperative measure. In view of the slow growth of untreated tumours, it was not possible to decide whether this postoperative treatment had had any effect. With regard to the cases in which the effect of roentgen

therapy could be assessed apart from the surgical treatment, three facts may be noted. First, complete or very satisfactory alleviation of pain was achieved in all patients; secondly, all the tumours except one showed a considerable decrease in size; and thirdly, a curative effect was not obtained in a single case.

Radiation treatment is thus indicated as a palliative in all cases that for one reason or another cannot be treated surgically. According to experiences recently reported in the literature, and our results in no way gainsay them, as large tumour doses as possible should be given. The largest dose that we delivered to the centre of the tumour in one treatment series was about 4 000 r in 29 days (Case 8). One of the best results in this material was obtained with this treatment. In all probability this dose cannot be exceeded with the conventional apparatus used almost without exception in the present material. Much larger doses can be delivered with the million volt technique, owing to the decrease in both skin and volume doses and in bone absorption. It remains to be seen whether a permanent cure can be effected by radiologic means with this technique.

Our experience of pre-operative roentgen treatment is limited to one case. In this a dose of about 3 500 r in 26 days was applied to the tumour centre. The operation was performed 10 weeks later and was not histologically radical. A recurrence occurred 18 months later.

There are many indications that pre-operative roentgen therapy, if correctly applied, increases the chances of achieving radical surgical intervention. According to our observations the tumours decrease in size after treatment with large roentgen doses, and clinical experience in many quarters has demonstrated that in the radiologic treatment of other types of malignant tumour the periphery of the tumour succumbs first while the centre is more radioresistant. This feature has been confirmed histologically in cancer of the uterus and of the rectum (Heyman, Hultborn). It is very probable, although not confirmed, that all malignant tumours, and hence chordomas as well, react to radiologic treatment in the same way. Pre-operative radiation ought therefore to be capable of facilitating surgical intervention. As chordomas are relatively radioresistant a depth dose of 3 000 to 4 000 r is probably required: with conventional roentgen therapy, such doses probably delay post-operative healing of the wound. With the million volt technique, the risks in this respect would seem to be much smaller; among other things, the skin dose is much reduced. Pre-operative radiation does not, however, free the surgeon from the necessity of excising a fair margin of healthy tissue.

The effect of postoperative radiation was difficult to assess in our material. Seven patients received roentgen therapy directly after the operation. The roentgen doses were much smaller than in the other

cases given radiation treatment. It was naturally impossible, in the individual cases, to distinguish between the effect of the roentgen therapy and the effect of the operation. Two patients are still living, and without recurrence, but the observation time is still too short to permit final judgment; 3 patients are alive but have recurrences; two patients died 4 years and 3 months, respectively, after the treatment.

Postoperative roentgen treatment of chordoma is in theory not particularly attractive. In patients who have already received adequate pre-operative radiation, postoperative treatment cannot be applied, as doses of significance can then no longer be given. Some doubt must also be felt regarding cases which have not received pre-operative treatment. The object of postoperative therapy would be to eliminate any tumour residues still existing. This means that one would be treating a very large area in the dark. Under such conditions a sufficiently large and homogeneous dose could not be achieved with conventional roentgen therapy. The possibilities have probably improved since million volt apparatus have become available. The effect of the therapy is reduced by the fact that the treatment area to a large extent would include cicatricial tissue, in which, according to experience, any tumour tissue that is present is more radioresistant than tumour tissue in its 'natural' environment.

The treatment of chordoma in children by radiation presents special problems. In our opinion, it has not been positively established that chordomas occurring in children are more radiosensitive than other chordomas. The advantages and disadvantages of a course of roentgen therapy should be carefully weighed in each case. It should always be remembered that roentgen treatment is followed by a fairly high degree of disability, owing to the effects of radiation on the growth zones of the skeleton and, in the case of sacrococcygeal chordomas, on the sexual glands.

In the treatment of chordomas by radiotherapy, there is every likelihood that much higher tumour doses will be used in the future, especially when the aim is curative. The advantages offered by supervoltage therapy, in the form of reduced skin doses, decreased bone absorption, and more homogeneous depth doses, are obvious and the preliminary results reported by BAKER & COLEY and FRIEDMAN are an incentive to continued effort. Roentgen doses of such a size as will be employed will, however, expose adjacent organs to great risks. In the case of sacrococcygeal chordoma, the rectum lies in the danger zone and the dosage should be continuously checked with a dosemeter within its lumen. In chordoma of the cervical, thoracic and upper lumbar spine, the proximity of the spinal cord should be borne in mind. Careful depth dose determinations should in general be made in connection with every form of radiologic treatment in chordoma.

SUMMARY

The surgical and roentgen treatments of chordoma are discussed in detail with special reference to a material of 16 proved cases of this growth. Chordomas react to large roentgen doses but there seems to be little hope of achieving a curative effect with conventional roentgen techniques; the advantages of the million volt technique are considered. Pre-operative roentgen therapy seems to be theoretically attractive whereas postoperative treatment would appear to offer less chances of success.

ZUSAMMENFASSUNG

Die Chirurgie und die Strahlentherapie der Chordome wird unter besonderer Bezugnahme auf ein Material von 16 verifizierten Fällen dieser Tumorform eingehend besprochen. Chordome reagieren auf hohe Röntgendosen; es scheint jedoch wenig Aussicht zu bestehen, mit konventioneller Röntgentechnik einen kurativen Effekt zu erzielen. Die Vorteile der Millionenvolt-Technik werden erwähnt. Präoperative Röntgentherapie scheint theoretisch lockend zu sein, während postoperative Behandlung weniger erfolgversprechend zu sein scheint.

RÉSUMÉ

Les auteurs étudient en détail le traitement chirurgical et roentgenthérapique du chordome, en se basant en particulier sur une série de 16 cas vérifiés. Les chordomes réagissent à de fortes doses de rayons roentgen, mais il semble y avoir peu d'espoir d'arriver à un effet curatif par les techniques classiques de roentgenthérapie; les auteurs examinent les avantages de la technique à un million de volts. La roentgenthérapie pré-opératoire semble théoriquement séduisante, alors que le traitement post-opératoire paraîtrait offrir moins de chances de succès.

REFERENCES

Baker, H. W. and Coley, B. L.: Chordoma of lumbar vertebra. J. Bone Jt Surg. 35 (1953), 403.

Dahl, O. and Vikterlöf, K. J.: Dose distribution in arc therapy in the 200 to 250 kV range. Acta radiol. (1958). Suppl. No. 171.

Dahlin, D. C. and MacCarty, C. S.: Chordoma. A study of fifty-nine cases. Cancer 5 (1952), 1170.

Fletcher, E. M., Woltman, H. W. and Adson, A. W.: Sacrococcygeal chordomas. A clinical and pathologic study. Arch. Neurol. Psychiat. 33 (1935), 283.

Friedman, M.: Technique of treatment of chordoma of a lumbar vertebra with 2 million volt X-rays using the rotation technique. Bull. Hosp. Joint Dis. 14 (1953), 180.

Heyman, J.: Die Radiumbehandlung des Uteruskrebses. Arch. Gynäk. 108 (1918). 229.

Hultberg, S., Dahl, O., Thoraeus, R. und Vikterlöf, K. J.: Das Kilocurie-Kobaltgerät des Radiumhemmet, genannt das Gammatron. *In:* Betatron und Telekobaltherapie. Springer-Verlag, Berlin-Göttingen-Heidelberg 1958.

Hultborn, K. A.: Cancer of the colon and rectum. Acta chir. scandinav. Suppl 172 (1952).

K[illegible]Y, E. und BERVEN, E.: Über maligne Chordome. Dtsch. Z. Chir. 225 (1930), 354.
L[illegible]DBOM, Å.: Personal communication.
M[illegible]cCARTY, C. S., WAUGH, J. M., MAYO, C. W. and COVENTRY, M. B.: The surgical treatment of presacral tumors. Proc. Staff Meet. Mayo Clin. 27 (1952), 73.
M[illegible]NTGOMERY, A. H. and WOLMAN, I. J.: Sacrococcygeal chordomas in children. Amer. J. Dis. Child. 46 (1933), 1263.
S[illegible]DAHL, C.: Case of chordoma malignum sacro-coccygeale. Acta chir. scandinav. 72 (1932), 421.
S[illegible]CKELFORD, R. T. and ROHDE, C. M.: Sacrococcygeal chordoma. Ann. Surg. 141 (1955), 952.
U[illegible]E, J. R. and PUGH, D. G.: Roentgenologic aspects of chordoma. Amer. J. Roentgenol. 74 (1955), 593.
W[illegible]OD, E. W.: Roentgenologic diagnosis and treatment of chordoma. Trans. Amer. Neurol. Ass. 75 (1950), 17.

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CIRCULATION THROUGH THE ANTERIOR COMMUNICATING ARTERY STUDIED BY CAROTID ANGIOGRAPHY

by

Georg-Fredrik Saltzman

Anatomical investigations have shown that the anterior communicating artery is rarely absent and hence the necessary conditions for the circulation through this vascular communication are usually present. By compressing the carotid artery on the opposite side to that on which the contrast medium has been injected it is possible angiographically to test whether the passage through the anterior communicating artery is free. This method of examination has proved to be of great value in neurosurgery, particularly in cases where there is a risk that the normal blood supply may be cut off. All neuroradiologists know, however, that not infrequently can both the pericallosal arteries be demonstrated at carotid angiography without any compression. The aim of the present paper is to study some of the factors influencing this 'spontaneous' passage of contrast medium through the anterior communicating artery in normal and pathologic conditions.

The material used for this investigation comprised 1 020 'conventional' carotid angiographies and 232 rapid serial carotid angiographies in which no vascular changes could be demonstrated. In addition, 223

Submitted for publication 27 January 1959.

angiographies performed in cases of intracranial expansive lesions and 11[illegible] angiographies in cases of arterial aneurysm were analyzed. The material is the same as that studied in another connection from the viewpoint of the demonstration of the posterior cerebral artery.

The statistical analyses were carried out by STAFFAN EKBLOM. Ordinary statistical methods were used, and the significance levels have been denoted as follows:

$0.05 > p > 0.01$ almost significant
$0.01 > p > 0.001$ significant
$0.001 > p$ highly significant

(By p is meant the probability that a difference between two values is due to chance.)

Conventional carotid angiographies without vascular lesions

Among 1 020 conventional carotid angiographies passage through the anterior communicating artery, *i. e.* filling of both the pericallosal arteries, was noted in 354 cases (34.7 ± 1.5 %). The incidence was exactly the same as for the demonstration of the posterior cerebral artery in the same material. The passage of contrast medium through the anterior communicating and posterior communicating arteries has often been established simultaneously, but by no means always.

The distribution on the two sides was unexpected. Among 481 angiographies of the right carotid artery both pericallosal arteries were shown in 142 (29.5 ± 2.1 %), while the corresponding figure for the 539 angiographies of the left carotid was 211 (39.1 ± 2.1 %). The difference is significant. No reasonable explanation of this difference has been found.

The sex distribution was also surprising. Among 537 carotid angiographies in men both the pericallosal arteries were shown in 214 (39.9 ± 2.1 %), while the corresponding figure among 483 women was only 137 (28.4 ± 2.1 %). The sex difference is highly significant, and as difficult to explain as the side difference.

When the material was divided into 10-year age groups no difference in incidence as regards the demonstration of both pericallosal arteries was noted. Nor was any appreciable difference obtained in larger groups. Both pericallosal arteries were visible in 179 (35.0 ± 2.1 %) out of 512 carotid angiographies in patients under 40 and in 173 (34.1 ± 2.1 %) out of 508 such examinations in patients over 40. The difference is not significant.

In the 146 cases in which 'normal' conventional carotid angiographies were carried out on both sides in the same patient, passage of contrast medium through the anterior communicating artery was established in

92 of the 292 examinations (31.5 ± 2.7 %). The figure is slightly lower than the corresponding figure for the whole material. In 67 cases (45.9 ± 4.1 %) there were no signs that contrast medium had passed through the anterior communicating artery on either side. Demonstration of both the pericallosal arteries was obtained at carotid angiography on the one side but not on the other in 66 instances (45.2 ± 4.1 %) and in 13 cases (8.9 ± 2.4 %) both these arteries were visible at carotid angiography on both sides.

The last-named 13 cases are of particular interest. In these, contrast medium was passed in both directions through the anterior communicating artery without carotid compression. It may seem tempting to explain this, as well as certain observations concerning the demonstration of the posterior cerebral artery, as a pressure increase on the side on which the injection was done, due to injection of the contrast medium. GREITZ, however, was not able to demonstrate any increase in pressure when making intravascular pressure measurements in connection with carotid angiographies. This passage of contrast medium in both directions may possibly have some connection with the anatomy of the anterior communicating artery. The communication between the two anterior cerebral arteries shows much variation. It does not always have the shape of a blood vessel. The two anterior cerebral arteries sometimes lie close together, the communication between them then having the appearance of a hole in a common 'septum'. It is not unlikely that blood passes through such an opening in both directions. I observed this variant in 3 out of 30 autopsies, when examining the circle of Willis. This incidence is of the same magnitude as the number of cases in which contrast medium passed through the anterior communicating artery in both directions. KLEISS, however, observed it in less than 1 % of his cases.

Comparing how contrast medium had passed through the anterior communicating artery in right- and left-sided angiographies it was found that the left-sided examinations showed a preponderance in this part of the material also. The medium had passed through in 40 (27.4 ± 3.7 %) on the right side and in 52 (35.6 ± 4.0 %) on the left side. The difference is not significant, however.

Site of puncture. The passage of contrast medium through the anterior communicating artery was also studied in internal carotid and common carotid angiographies. By common carotid angiography is meant here all those examinations in which contrast medium could be seen not only in the internal carotid artery but also in the external carotid, even if the medium had been injected into the internal carotid.

The medium had passed through the anterior communicating artery in 262 out of 597 internal carotid angiographies (43.9 ± 2.0 %) and in

92 out of 423 common carotid examinations (21.7 ± 2.0 %). The difference is highly significant.

In 21 instances the substance was injected into both internal and common carotid arteries on the same side. Sixteen of these examinations showed similar features irrespective of the site of injection while in 5 the medium passed through the anterior communicating artery at internal carotid but not at common carotid angiography. The opposite features were not observed in a single case.

Complications on carotid puncture. Even the most experienced neuroradiologist cannot avoid occasional complications in the form of haematomas or extravascular injection of the contrast medium when puncturing for carotid angiography. These complications seem to affect the passage of the contrast medium through the anterior communicating artery.

As in the case of the posterior cerebral artery, the significance of haematomas was studied in an unselected angiographic material consisting of 100 examinations carried out in succession. Only haematomas observed before injection of contrast medium were recorded. The incidence of haematoma was higher than usual in this material. Of 31 cases with haematoma, passage of contrast substance through the anterior communicating artery was established in 9 (29.0 ± 8.2 %), and in 69 without this effusion the corresponding figure was 29 (42.0 ± 5.9 %). The difference is not significant in this small series.

Extravascular injection of contrast medium occurred in 101 instances among 1 020 'normal' conventional carotid angiographies. Passage of contrast medium through the anterior communicating artery was established in 18 of these (17.8 ± 3.8 %). The difference as against the whole material is highly significant.

In 14 (13.9 ± 3.4 %) of the 101 examinations where contrast medium had been injected extravascularly, not even the anterior cerebral artery on the injected side was visible. (By the anterior cerebral artery is meant the vessel segment between the bifurcation of the internal carotid artery and the origin of the anterior communicating artery. Distal to this segment the main trunk of the vessel is called the pericallosal artery.) In the other 919 cases this finding was recorded only 11 times (1.2 ± 0.4 %). The difference is highly significant. The anterior cerebral artery may be narrow, or wholly absent, but the latter anomaly is extremely rare. It may also be thrombosed, but this is unusual. Among the 11 cases in which no extravascular injection had occurred, the anterior cerebral artery was very narrow in 4 after compression of the carotid artery on the opposite side. In 2 instances, the anterior cerebral artery was not even filled after compression of the carotid artery on the opposite side. It is beyond all doubt that, in the vast majority of 'normal' cases, in-

complete filling of the anterior cerebral artery is directly connected with puncture complications, as WICKBOM, RUGGIERO, and RIISHEDE have already pointed out.

As in the investigation on the posterior cerebral artery (SALTZMAN), I studied the way in which contrast medium passed through the anterior communicating artery in those patients in whom internal carotid or common carotid angiography had been preceded by an injection of contrast medium into the external carotid artery. Among 152 examinations of this type the substance flowed through in 53 (34.9 ± 3.9 %). There was no significant difference between the total material and these cases in which an external carotid examination had preceded internal or common carotid angiography.

Blood pressure measurements were carried out immediately before carotid angiography in 100 instances. The patients were divided into two groups, those with a systolic blood pressure of up to 140 mm Hg forming the one group and those with 145 mm Hg and upwards the other. Each group contained 50 patients. In the former group passage of contrast medium through the anterior communicating artery was established in 19 instances (38.0 ± 6.9 %) and in the latter in 16 (32.0 ± 6.6 %). The difference is not significant.

The influence of general anaesthesia, which usually has a depressing effect on the blood pressure, on the passage of contrast medium through the anterior communicating artery was also investigated. Anaesthesia was given in connection with 87 'normal' conventional carotid angiographies. Passage of contrast medium was established in 32 of these (36.8 ± 5.2 %). The difference as against the whole material is not significant.

Rate of injection. The 63 patients in whom the injection rate was recorded were placed in two groups, namely, cases with injection times of over and under 2 seconds. Passage of contrast medium was established in 10 (34.5 ± 8.8 %) out of 29 cases with an injection time of over 2 seconds and in 12 (35.3 ± 8.2 %) out of 34 with a time of less than 2 seconds. The difference is not significant.

Rapid serial carotid angiographies without vascular changes

Among 232 rapid serial angiographies of the carotid artery, contrast medium had passed through the anterior communicating artery in 96 (41.4 ± 3.2 %). The incidence was higher than the corresponding figure for the conventional carotid angiographies. The difference is not significant, however.

The side distribution showed the same surprising tendency as in the conventional carotid angiographies. Passage through the anterior communicating artery was established in 35 out of 100 right-sided examinations (35.0 ± 4.8 %) and in 61 out of 132 left-sided examinations (46.2 ± 4.3 %). The difference is, however, not significant in this small material.

Sex difference such as were noted in the conventional angiographies were not observed here. There was passage of contrast medium through the anterior communicating artery in 52 out of 128 men (40.6 ± 4.3 %) and in 44 out of 104 women (42.3 ± 4.8 %). The difference is not significant.

As regards age distribution, 10-year groups gave figures too low to permit a statistical analysis in this material. A total of 113 patients were under 40 and 119 over 40 years of age. Contrast medium passed through the anterior communicating artery in 50 (44.2 ± 4.7 %) of those in the younger group and in 46 (38.7 ± 4.5 %) of those in the older group. The difference is not significant.

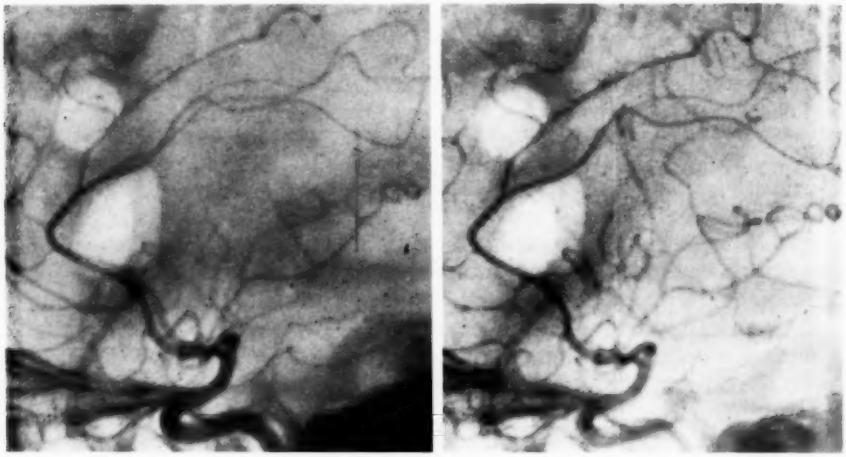
Contrast medium. Two contrast media, Triurol 50 % (sodium acetrizoate) and Hypaque 45 % (sodium diatrizoate), were used for these rapid serial angiographies. The Triurol solution contained about 20 % more iodine per unit of volume than the Hypaque solution.

Triurol was used in 86 examinations and Hypaque in 146. Passage of contrast medium through the anterior communicating artery was established in 27 instances in the Triurol group (31.4 ± 5.0 %) and in 69 in the Hypaque group (47.3 ± 4.1 %). The difference is significant. The cause of this difference is obscure. However, it definitely indicates that filling of both the pericallosal arteries is not connected with the concentration of the contrast medium.

Site of puncture. Among 232 rapid serial carotid angiographies the medium was injected into the internal carotid artery in 119 and into the common carotid in 113. Passage of contrast medium through the anterior communicating artery was established in 66 (55.5 ± 4.2 %) of the internal carotid and in 30 (26.6 ± 4.1 %) of the common carotid examinations. In both groups, the incidence was higher than in the conventional carotid angiographies. The difference is greater for the internal than for the common carotid group.

Duration of visibility of both pericallosal arteries. It is sometimes observed at a renewed carotid angiography under apparently the same conditions as before, that both the pericallosal arteries are visible after the one injection while only one of these two vessels fills at the next injection, or vice versa. As in the investigation on the posterior cerebral artery, the rapid serial angiographies provided an explanation of this finding.

It was noted that passage through the anterior communicating artery took place as long as contrast medium was visible in the carotid siphon, in only 42 out of 96 cases (43.8 ± 5.1 %). In the remaining 54 cases (56.3 ± 5.1 %) the contrast medium was visible in both pericallosal arteries only while injection was in progress. As soon as the injection was concluded the pericallosal artery on the opposite side was no longer seen despite the fact that the contrast density was still high in the carotid siphon. (See figure.)



a b

Rapid serial carotid angiography. While the injection is in progress (a) contrast medium is seen in both the pericallosal arteries. Immediately after the injection, no medium is seen in the pericallosal artery on the opposite side. The posterior cerebral artery also is visible during the injection but not after it has been concluded.

When these two groups of rapid serial angiographies were divided up among internal carotid and common carotid examinations the following distribution of the cases was obtained. Among 66 internal carotid angiographies, contrast medium passed through the anterior communicating artery only during the actual injection in 42 (63.6 ± 5.9 %) while in 24 (36.4 ± 5.9 %) it continued to flow through the artery as long as there was contrast medium in the carotid siphon. Among 30 common carotid angiographies, the corresponding figures were 12 (40.0 ± 8.9 %) and 18 (60.0 ± 8.9 %). The difference is almost significant. It was thus mainly in the internal carotid angiographies that this transient passage through the anterior communicating artery, closely bound up with the injection period, was observed.

Table 1

Passage of contrast medium through anterior communicating artery demonstrated in cases of intracranial expansive processes at different sites

Site of lesion	Number of cases	Passage demonstrated in: Number of cases	Percentages
Frontal	96	26	27.1 ± 4.5
Parietal	43	13	30.2 ± 7.0
Temporal	45	17	37.8 ± 7.2
Central	22	5	22.7 ± 8.9
Others	17	5	29.4 ± 11.1
Total	223	66	29.6 ± 3.1

Intracranial expansive processes

The material includes 223 conventional carotid angiographies performed on the side where an expansive process had been situated or was most extensive. Passage of contrast medium through the anterior communicating artery was established in 66 of these (29.6 ± 3.1 %). The incidence is slightly lower than in the normal material but the difference is not significant.

When the material was divided among internal carotid and common carotid angiographies the same difference was obtained for passage through the anterior communicating artery, with a higher incidence in the internal carotid than in the common carotid angiographies. Contrast medium passed through the anterior communicating artery in 38 (37.6 ± 4.8 %) out of 101 internal carotid angiographies and in 28 (23.0 ± 3.8 %) out of 122 common carotid examinations. The difference between the two types of angiography is almost significant.

Site of lesion. The expansive processes have been roughly classified, according to their site, into frontal, parietal, temporal, and central lesions. In another group designated 'Others' were placed odd cases of occipital, cerebellar and multiple processes as well as lesions covering such a large part of the brain that they did not obviously belong to any particular group. The incidence of passage through the anterior communicating artery for the different sites may be seen from Table 1.

The figures differed from the corresponding figures obtained for the posterior cerebral artery (SALTZMAN). Whereas the incidence for passage through the anterior communicating artery was highest among the temporal and lowest among the central lesions, the opposite was the case with respect to the posterior cerebral artery. The differences are not significant, however.

Table 2

Passage of contrast medium through anterior communicating artery in cases of intracranial expansive processes of different types

Nature of lesion	Number of cases	Passage demonstrated in: Number of cases	Percentages
Glioma	96	29	30.2 ± 4.7
Meningioma	41	9	22.0 ± 6.5
Intracerebral haemorrhage	26	7	26.9 ± 8.7
Others	32	13	40.6 ± 8.7
Expansive lesions of undiagnosed type	28	8	28.6 ± 8.5
Total	223	66	29.6 ± 3.1

Type of lesion. The classification of the expansive processes according to their nature was also rough, the number of groups being kept as small as possible. The gliomas were not divided into subgroups. In a group marked 'Others' were placed a number of fairly uncommon expansive lesions such as metastases, abscesses, cysts, angiomas, sarcomas, cholesteatomas, and tuberculomas. There were no subdural haematomas in the material. The incidence of filling of both pericallosal arteries in the different groups is shown in Table 2.

Only the incidence in the group marked 'Others' showed any appreciable deviation from the average incidence. This group is, however, too heterogeneous to permit conclusions to be drawn from it.

[Arterial aneurysm]

Passage through the anterior communicating artery was recorded in 37 (31.4 ± 4.3%) out of 118 conventional carotid angiographies showing arterial aneurysm. The figure is slightly lower than that obtained in the conventional carotid angiographies without vascular lesions. The difference is not significant.

Of these examinations, 62 were internal carotid and 56 common carotid angiographies. Contrast medium passed through the anterior communicating artery in 25 (40.3 ± 6.2 %) of the former and in 12 (21.4 ± 5.5 %) of the latter. Here also, we find the same difference between internal carotid and common carotid angiographies as in the conventional carotid examinations showing no vascular changes.

Table 3

Passage of contrast medium through anterior communicating artery in cases of arterial aneurysm at different sites

Site of the aneurysm	Number of cases	Number of cases	Passage demonstrated in: Percentages
At origin of post. comm. artery	33	5	15.2 ± 6.5
At bifurcation of int. carot. artery	7	1	
At origin of ant. comm. art. in ant. cerebral artery	40	22	55.0 ± 7.9
In middle cerebral artery	32	5	15.6 ± 6.4
In pericallosal artery	4	3	
In extradural part of int. carot. artery	2	—	
All cases of aneurysm	118	37	31.4 ± 4.3

Site of aneurysm. Aneurysms are usually situated close to vascular bifurcations. The distribution as to site is shown in Table 3.

The three largest groups are composed of aneurysms at the site where the posterior communicating artery leaves the internal carotid artery, aneurysms at the origin of the anterior communicating artery in the anterior cerebral artery, and finally, aneurysms of the middle cerebral artery. These three groups were the only ones large enough to permit a statistical analysis. In Table 3 the incidence of established passage through the anterior communicating artery in the different groups is recorded.

The variations are remarkable. The cases with aneurysm at the origin of the posterior communicating artery in the internal carotid artery, as well as those with aneurysm of the middle cerebral artery show a low incidence for filling of both the pericallosal arteries, whereas, on the other hand, cases with aneurysm at the site where the anterior communicating artery leaves the anterior cerebral artery show the highest incidence that has hitherto been recorded. The difference between the incidence in the latter group and that in the other main groups is highly significant.

The 25 cases in which aneurysm was present at the origin of the anterior communicating artery in the anterior cerebral artery and in which bilateral carotid angiography had been performed were analyzed in more detail. The anterior cerebral artery was not visible at all in 11 (44.0 ± 9.9 %) of the 25 angiographies performed on the opposite side from the aneurysm. Comparing this figure with the normal material, after deduction of the examinations in which extravascular injection of contrast medium

had occurred, we found non-filling of the anterior cerebral artery in 1 out of 919. The difference is highly significant. Even when the angiographies with extravascular injection, in which the incidence of non-filling of the anterior cerebral artery was high, were included, the difference was still highly significant.

Conclusions

Passage of contrast medium through the anterior communicating artery was demonstrated without compression in more than one-third of our conventional carotid angiographies showing no vascular lesions. This observation is of some practical significance. In those cases in which filling of the pericallosal artery on one or both sides has been established at carotid angiography on the opposite side, the presence of a communication between the vascular systems of the two halves of the brain has been confirmed. No further injection of contrast medium with carotid compression is necessary. It should be stressed, however, that passage through the anterior communicating artery does not alone prove that there is free communication between the two halves of the brain, since the anterior cerebral artery on the opposite side may be absent or obliterated.

The incidence of passage through the anterior communicating artery was higher in the internal carotid than in the common carotid angiographies. As in the investigation on the posterior cerebral artery (SALTZMAN), it would seem tempting to explain this difference as a pressure increase due to the injection of the contrast medium, an increase greater in internal than in common carotid angiography. Arguments in favour of and against such a pressure increase have been discussed in connection with the demonstration of the posterior cerebral artery (GREITZ). It would be interesting to study the question in a larger material, with possibilities available for recording very small pressure differences.

Complications due to puncturing affect the circulation through the anterior communicating artery. Extravascular injection of the contrast medium, in particular, caused a decrease in the incidence of passage through the artery in our material. Without doubt, extravascular accumulations of contrast medium, and haematomas often exercise pressure on the carotid artery and consequently cause a pressure decrease distal to the artery. GREITZ observed in preliminary investigations that when the artery was compressed proximal to the puncture needle, on the side on which the injection was made, passage of contrast medium through the anterior communicating artery was inhibited; when the pressure was increased the anterior cerebral artery also ceased to be visible.

The general blood pressure level does not seem to affect the flow of

contrast medium through the anterior communicating artery. Nor does general anaesthesia have any significant effect on the passage.

A series of rapid serial carotid angiographies without vascular lesions showed a slightly higher incidence of filling of both the pericallosal arteries. This was above all noticeable in internal carotid angiographies. This must be placed in relation to the observation that in over one half of all cases passage through the anterior communicating artery can be established only while the actual injection of contrast medium is in progress, a phenomenon difficult to explain if the injection does not cause a pressure increase. In such cases a possible flow through the artery can easily fail to be detected in conventional angiographies, especially in the case of a rapid injection, when the time is short between the moment when the contrast medium reaches the anterior cerebral artery and the conclusion of the injection. Transient passage of this kind, closely connected with the injection time, is much more common in internal carotid than in common carotid angiographies.

In connection with rapid serial carotid angiography, we were able to compare two different contrast media with a slightly different iodine content per unit of volume. No difference as regards the passage through the anterior communicating artery was noted.

It would seem reasonable to expect that, as in the case of the posterior cerebral artery, passage through the anterior communicating artery would be more frequently observed with a rapid injection of contrast medium than with a slow one. No significant difference could be established, however.

In the light of these observations, certain guiding principles may be suggested for obtaining a high percentage of films showing passage through the anterior communicating artery, viz.:

1. The internal carotid artery should be punctured.

2. Rapid serial angiography is the examination of preference.

3. To avoid puncture complications an experienced operator should deal with those cases in which it is particularly necessary that passage of the contrast medium should be established.

In most cases in which it is important to establish the presence of a free communication between the vessels in both halves of the brain, carotid angiography is performed on both sides. If a higher incidence of films showing free passage through the anterior communicating artery can be achieved with an improved technique, the number of compression tests can be reduced, and consequently also the amount of contrast medium injected.

The incidence of filling of both the pericallosal arteries in intracranial expansive processes did not, in general, diverge significantly from the figure obtained in the normal material. Regarding the site of the processes it is, however, worthy of note that the incidence was higher than the average in temporal processes and lower in central processes. The incidence of filling of the posterior cerebral artery (SALTZMAN) with respect to these sites was the opposite. The nature of the processes had no significant effect on the passage of contrast medium through the anterior communicating artery.

In arterial aneurysm, remarkably large differences were noted in the incidence of filling of both pericallosal arteries. The incidence was low when the aneurysm was situated at the origin of the posterior communicating artery in the internal carotid artery, or in the middle cerebral artery. It is highly probable that this has some connection with the vascular spasm often observed by ECKER & RIEMENSCHNEIDER, and by LÖFSTEDT, in arterial aneurysm.

When the aneurysm was situated at the origin of the anterior communicating artery in the anterior cerebral artery the incidence was higher than in any other part of the material. This accords with the observation made regarding the passage of contrast medium through the posterior communicating artery in aneurysm at the site where the latter vessel leaves the internal carotid artery. Histologic examination of the vessel wall may possibly provide an explanation of the phenomenon. There may conceivably be defects in the unstriped muscle of the communicating arteries (HASSLER & SALTZMAN) close to these aneurysms. This could explain why the spasm probably responsible for the lower incidence of films showing passage through the communicating arteries when the aneurysm lies farther away, does not often occur here. Histologic investigations to clear up this problem are being planned.

In those cases in which aneurysm was observed at the origin of the anterior communicating artery, carotid angiography on the opposite side often revealed incomplete filling of the anterior cerebral artery. There was no filling of this vessel in nearly one half of these examinations on the opposite side. Such a finding is extremely unusual, unless the puncture has been complicated by haematoma or extravascular injection of contrast medium. Hence, if non-filling of the anterior cerebral artery is noted at a carotid angiography without puncturing complications, this must be an indication for performing a carotid angiography on the opposite side.

SUMMARY

The incidence of passage of contrast medium through the anterior communicating artery was studied in a series of 1 020 conventional carotid angiographies without vascular lesions, 232 rapid serial carotid angiographies in patients with intracranial expansive processes, and 118 conventional carotid angiographies in patients with arterial aneurysm. Internal carotid angiographies were compared with common carotid angiographies. The effect of complications arising from the puncturing procedure, and of the blood pressure, was also investigated. Rapid serial angiographies were compared with conventional angiographies. The passage of contrast medium was studied in expansive intracranial processes of different types and sites. The incidence of this finding was studied in arterial aneurysm, chief interest being concentrated on the site of the aneurysm.

ZUSAMMENFASSUNG

Das Vorkommen einer Kontrastpassage durch die Arteria communicans posterior wurde an einem Material von 1 020 konventionellen Karotisangiographien ohne Gefässveränderungen, an 232 mit schnellen Bildwechsel durchgeführten Karotisangiographien bei Patienten mit intrakraniellen expansiven Prozessen und an 118 konventionellen Karotisangiographien bei Patienten mit arteriellen Aneurysmen studiert. Karotis interna-Angiographien wurden mit üblichen Karotisangiographien verglichen. Der Effekt von Komplikationen, welche durch die Punktion entstehen, sowie von Blutdrucksveränderungen wurde ebenfalls untersucht. Mit schnellen Bildwechsel angefertigte Angiographien wurden mit konventionellen Angiographien verglichen. Die Passage des Kontrastmittels wurde bei expansiven intrakraniellen Prozessen verschiedener Typen und Lokalisationen untersucht. Das Vorkommen dieses Befundes wurde bei arteriellen Aneurysmen studiert; hierbei wurde das Interesse hauptsächlich auf die Lokalisation des Aneurysmas konzentriert.

RÉSUMÉ

L'auteur a étudié la fréquence du passage du moyen de contraste à travers l'artère communicante antérieure sur une série de 1 020 angiographies carotidiennes classiques sans lésion vasculaire, 232 angiographies carotidiennes en série rapide chez des malades atteints de processus expansifs intracraniens, et 118 angiographies carotidiennes classiques chez des malades porteurs d'anevrismes artériels. Il a comparé les angiographies par la carotide interne avec les angiographies par la carotide primitive. L'effet des complications dues a la ponction et de la pression sanguine est aussi étudié. Les angiographies en série rapide sont comparées aux angiographies classiques. Le passage du moyen de contraste à travers l'artère communicante antérieure a été étudié dans des processus expansifs intracraniens de types et de sièges divers. La fréquence de ce passage a été étudié dans les anévrismes artériels, en tenant spécialement compte du siège des anévrismes.

REFERENCES

ECKER, A. and RIEMENSCHNEIDER, P. A.: Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysm. J. Neurosurg. 8 (1951), 660.

GREITZ, T.: A radiologic study of the brain circulation by rapid serial angiography of the carotid artery. Acta radiol. (1956) Suppl. 140.
— Unpublished data.
HASSLER, O. and SALTZMAN, G. F.: Histologic changes in infundibular widening of the posterior communicating artery. Acta path. microbiol. scand. In press.
KLEISS, E.: Die verschiedenen Formen des Circulus arteriosus cerebralis Willisi. Anat. Anz. 92 (1942), 216.
LÖFSTEDT, S.: Angiography in intracranial arterial aneurysms. Paper read at the Third Symposium Neuroradiologicum, Stockholm 1952. (Not published.)
RIISHEDE, J.: Cerebral apoplexy. Acta psychiat. neurol. scand. (1957) Suppl. 118.
RUGGIERO, G.: Factors influencing the filling of the anterior cerebral artery in arteriography. Acta radiol. 37 (1952), 87.
SALTZMAN, G. F.: The angiographic demonstration of the posterior communicating and posterior cerebral arteries. I. Normal angiography. II. Pathologic angiography. Acta radiol. 52 (1959), 1, 114.
WICKBOM, I.: Angiography of the carotid artery. Acta radiol. (1948) Suppl. No. 72.

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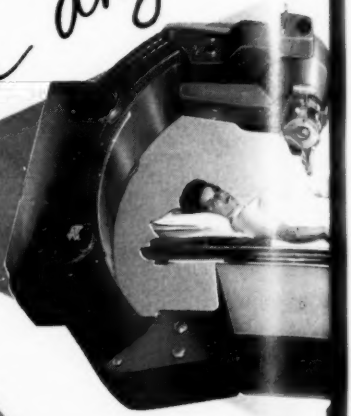

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CHANGES IN THE AMBIENT WING CISTERNS SECONDARY TO INTRACRANIAL MASSES

by

Alfred L. Schmitz

The first anatomic description of the region of the ambient wing cistern was that of KEY and RETZIUS in 1875. LOCKE and NAFFZIGER subsequently demonstrated this cistern by means of a cast of the ventricular and subarachnoid spaces and pointed out the close relationship of the cistern to the ventricular system. Unfortunately, their excellent model did not lend itself well to reproduction. This structure was labeled the cisterna intercommunicans by DAVIDOFF and DYKE without further discussion. It was later thoroughly investigated by LILIEQUIST who called it the ambient wing cistern, and this terminology will be used here. Interest in this region has most recently been opened by AZAMBUJA, LINDGREN and SJÖGREN as an adjunct in the diagnosis of tentorial slit herniations.

As demonstrated by LILIEQUIST, the normal ambient wing cisterns are a portion of the subarachnoid space situated around the thalamus. They are perpendicular to the ambient cistern proper, and extend from its anterior superior edge. These wings are situated in a curved frontal plane. They continue above the thalamus and below the fornices as far as the foramen of Monro. Laterally, the wings extend to the attachment of the choroid plexus. The wings communicate above the roof of the third

ubmitted for publication 21 March 1959.

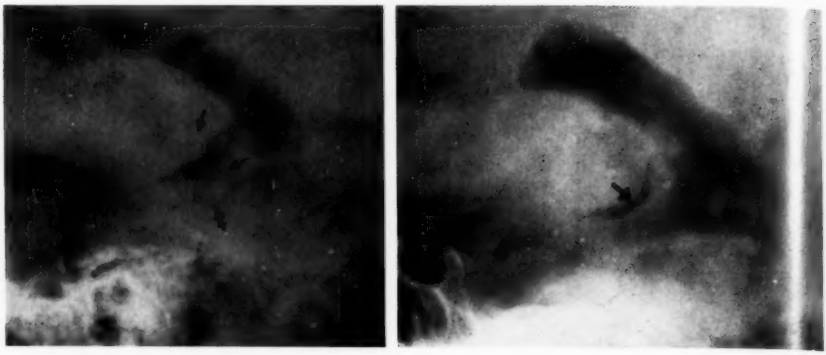

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Fig. 1. a) Normal lateral. The ambient wing cisterns cross the mid-quadrigeminal plate. The pericallosal cistern extends from the upper ambient wing cistern in a posterior direction and curves superiorly in an arc over the splenium. The air above the anterior superior cerebellum (‡) forms an arc concavity facing postero-inferiorly, with the quadrigeminal plates (†) lying above and anteriorly. b) Normal lateral. Ambient wing cisterns are anterior to the trigone.

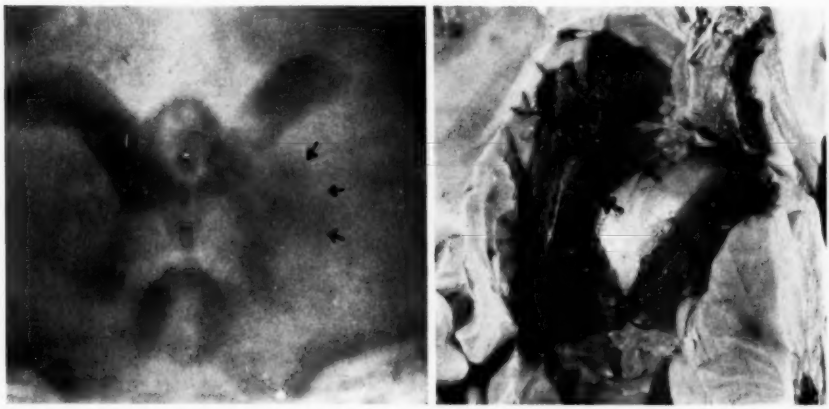

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Fig. 2. a) Half axial p. a. view. Normal ambient wing cistern extending laterally from the upper anterior brain stem. b) Posterior dissection of the lateral ventricle and pulvinar thalamus. Ventricle and ambient wing cisterns separated by velum interpositum (about 1 mm thick).

ventricle with each other, and behind the thalamus with the quadrigeminal cistern. The anterior concave surface borders the thalamus. The posterior convex surface borders the fornix. The inferior portion borders the hippocampal gyrus and the wing terminates anteriorly against the posterior edge of the uncus.

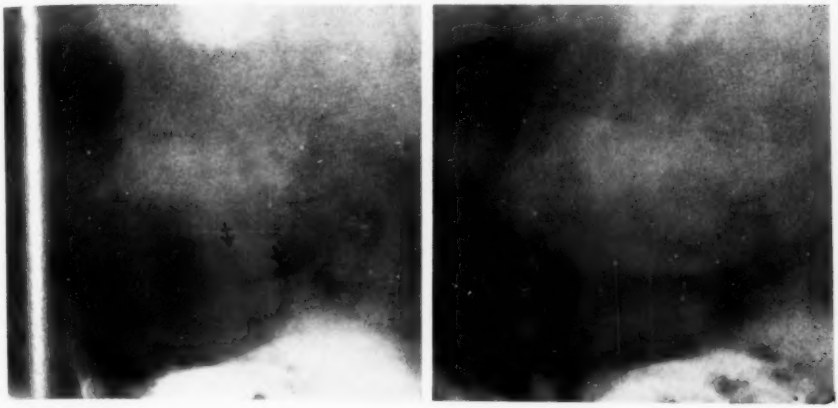

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Fig. 3. a) Left parietal tumor. Normal right anterior temporal horn filled (‡). Left ambient wing cistern displaced inferiorly (↓). b) Left temporal horn and ambient cistern filled, confirming downward displacement.

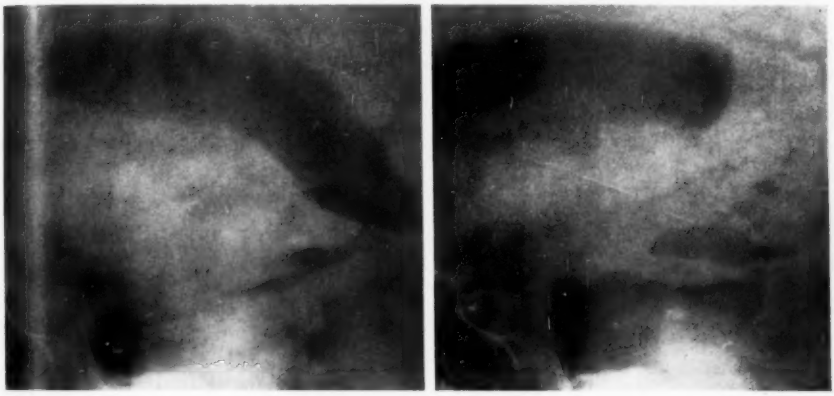

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Fig. 4. a) Right temporal tumor. Normal left wing cistern. Posterior superior displacement of right wing cistern. b) Filling of both anterior temporal horns confirming the posterior superior displacement on the right.

In life the ambient wing cistern can best be demonstrated by encephalography. On lateral films of the skull the two wings are superimposed and appear concave anterosuperiorly. They outline the posterior portions of the pulvinar thalamus. They cross the quadrigeminal plate at the level of its midportion or somewhat superiorly (Fig. 1a). An anterior medial

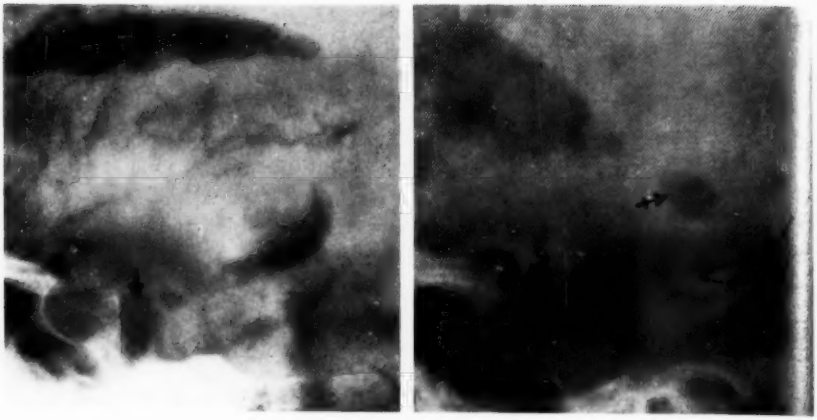

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Fig. 5. a) Tumor in region of third ventricle. Obliterated interpeduncular cistern (↓) with equivocal displacement of the ambient wing cisterns. b) Composite picture: ambient wing cisterns displaced posteriorly and inferiorly. Compressed suprasellar cistern (↗), elevated and grossly deformed third ventricle (↑).

extension of the cistern over the roof of the third ventricle is at times demonstrated. Occasionally the midline splenial portion of the pericallosal cistern can be seen extending posterior to the upper ambient cistern taking an upward course as it curves around the splenium of the corpus callosum. The gas around the anterior superior aspect of the cerebellum forms an arc, concave postero-inferiorly. The quadrigeminal plate lies just anterior to and above this level. The ambient wings are situated just anterior to the trigone of the lateral ventricle, an important relationship (Fig. 1b). Large ambient wings can occasionally be seen on a frontal view exposed with the central ray approximately perpendicular to the tentorial slit (Fig. 2a). They extend laterally from the upper anterior portion of the brain stem and outline the pulvinar. At their lateral margins they are separated from the lateral ventricles by no more than a millimeter of tissue, the velum interpositum (Fig. 2b).

Dislocations of the ventricular system by tumor in the region of the trigone are accompanied by dislocation of the ambient wing cistern. The direction of displacement reflects the direction of the force. For example, a tumor superior to the wing causes an inferior displacement (Fig. 3a), and one inferiorly causes a superior displacement (Fig. 4a). These changes can be confirmed by filling the ventricular system (Figs 3b and 4b). In the event that the ventricular system cannot be filled on the diseased side, comparison of the position of the displaced ambient

Fig. 6. Posterior temporal herniation. Posterior inferior displacement of the wing cisterns, posterior portion of the pericallosal cistern (‡) and quadrigeminal plates, the latter showing greatest displacement. Herniation deforms upper anterior portion of the cerebellum (ϟ).

wing cistern with that of the normal wing or ventricle is of great diagnostic import. If all lateral projections are taken with the same magnification and positioning, composite tracings made from the different projections of the ventricular system and cisterns may give additional information. Fig. 5 illustrates a central midline tumor where the ventricular system and ambient wing cisterns could only be filled separately giving equivocal information. A composite tracing shows the ambient wing cisterns to be displaced posteriorly by the effects of tumor pressure. This was confirmed at post mortem examination.

The ambient wing cistern may also be displaced by indirect pressure secondary to a herniation of the posterior portion of the temporal lobe through the tentorial slit. In our cases both ambient wings and quadrigeminal plates are displaced inferiorly through the tentorial slit. The displacement of the wing cisterns and quadrigeminal plate appears to take place in the form of a 'V' with the midline structure, the quadrigeminal plate, displaced more than the laterally situated ambient wing cisterns. This occurred in the case shown in Fig. 6 in spite of the fact that the posterior herniation was mainly unilateral. Thus, in our small series of pneumographically demonstrated posterior temporal lobe herniations, the anatomic details appear to differ from those previously reported. The deformation of the brain stem and the changes in the colliculate bodies were as previously described by AZAMBUJA, LINDGREN & SJÖGREN. Their statement that 'on the diseased side, the ambient wing cistern is projected over the lower half of the quadrigeminal plate' is not in conformity with our findings. This may be due to the fact that our cases are all without clinical evidence of increased intracranial pressure and with normal lumbar tap pressure readings.

As previously reported, posterior herniations can flatten the anterior superior surface of the cerebellum on the involved side. The air above the cerebellum in these cases loses its smooth curve and becomes angular. Where the normal concavity of this curve faces postero-inferiorly, it becomes flattened or the curve may be reversed (Figs. 6 and 7c). Some of the air over the cerebellum is lateral to the midline since it can be seen

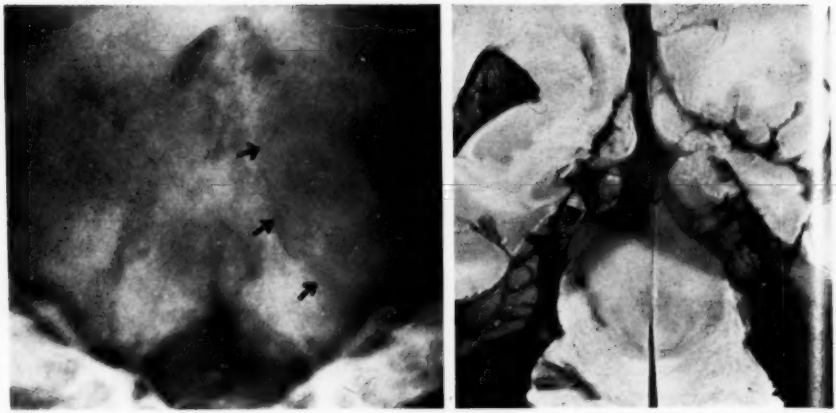

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Fig. 7.

a) Right posterior temporal herniation outlined by air. Brain stem flattened on the side of the herniation.

b) Anatomic specimen from same patient. Large right, small left posterior temporal herniation.

c) Same patient. Posterior temporal herniation with quadrigeminal plate showing greatest diplacement (←). Air outlines the hernaiation's lower edge (↑).

to cross the quadrigeminal plate, a midline structure. In my opinion this air outlines the undersurface of the herniated temporal lobe which also is somewhat lateral to the midline. This air may easily be misinterpreted as a displaced ambient wing cistern. In this regard, the herniated portion of the temporal lobe can also be seen in the half axial p. a. view projecting medially over the tentorium (Fig. 7a).

Posterior temporal herniations may cause a posterior inferior displacement of the lower part of the cistern about the splenium of the corpus callosum. In the case demonstrated in Fig. 6 there was invasion of the corpus callosum anteriorly by a tumor which caused an associated posterior temporal lobe herniation. The change in the wing cistern was thought due to a posterior extension of the tumor. Post-mortem disclosed

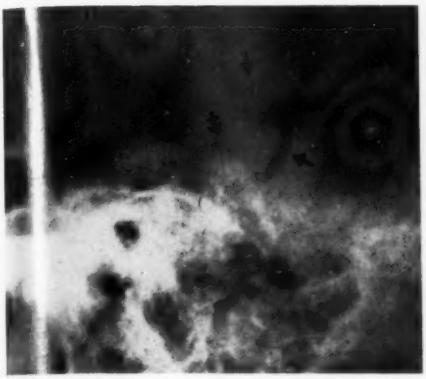

Fig. 8. Anterior and posterior temporal herniation. Quadrigeminal plates displaced posteriorly and inferiorly (↓) as judged by their relationship with the anterior surface of the deformed cerebellum (↕). The obliterated interpeduncular cistern indicates an anterior temporal herniation.

a normal splenium. The changes in the cistern were secondary to the herniation and not directly due to pressure by the tumor.

A combined herniation with displacement of the quadrigeminal plate and ambient wing cisterns (Fig. 7c) is also of interest in that the wing on the side of the large right posterior herniation was the least displaced posteriorly on post-mortem. The herniated right temporal lobe was interposed between the pulvinar and the posterior structures.

At times, information regarding the ambient wing cisterns may be obtained indirectly. The diagnosis of herniation may be made without demonstration of the ambient wings where there is a posterior inferior displacement of the quadrigeminal plates and a deformity of the upper cerebellar surface (Fig. 8). These changes become evident when they are compared with the normal.

This material illustrates that even severe temporal herniations may exist without clinical evidence of increased intracranial pressure and in these cases a technique utilizing complete exchange of fluid would in my opinion appear dangerous.

Acknowledgement

I wish to thank Dr. Robert B. Aird, Professor of Neurology, Dr. John E. Adams, Associate Professor of Neurological Surgery, Dr. Nathan Malamud, Clinical Professor of Psychiatry and Neuropathology, and the staff members of their departments for their cooperation and for the use of the clinical and pathologic material in the preparation of this paper.

SUMMARY

The normal ambient wing cistern and its anatomic relationship are discussed. Changes secondary to direct tumor pressure and those secondary to herniation of the posterior temporal lobe are described. These posterior temporal herniations existed in patients without a clinical diagnosis of increased intracranial pressure.

ZUSAMMENFASSUNG

Die normale Cisterna ambiens und ihre anatomischen Beziehungen werden diskut rt. Durch direkten Tumordruck bedingte sowie durch eine Hernie des Lobus tempo lis posterior verursachte sekundäre Veränderungen werden beschrieben. Diese hint en temporalen Brüche bestehen bei Patienten ohne klinische Diagnose eines erhöhten i ra-kraniellen Druckes.

RÉSUMÉ

L'auteur étudie l'aile de la citerne ambiante et ses rapports anatomiques. Il d rit ses modifications secondaires à une pression tumorale directe et secondaires à une h nie postérieure du lobe temporal. Ces hernies temporales postérieures existaient chez des malades pour lesquels on n'avait pas fait le diagnostic clinique d'hypertension i tra-cranienne.

REFERENCES

Azambuja, N., Lindgren, E. and Sjögren, S. E.: Tentorial herniations. Acta radiol. 46 (1956), 215.

Bassett, D. L.: A stereoscopic atlas of human anatomy. Section I. The central nervous system. Sawyer's, Portland 1954.

Davidoff, L. M. and Dyke, C. G.: The normal encephalogram. Second edition. Lea & Febiger, Philadelphia 1946.

Key, E. A. H. und Retzius, G.: Studien in der Anatomie des Nervensystems und des Bindegewebes. Samson & Waller, Stockholm 1875—76.

Liliequist, B.: The anatomy of the subarachnoid cisterns. Acta radiol. 46 (1956), 61.

Locke, Jr., C. E. and Naffziger, H. C.: The cerebral subarachnoid system. Arch. Neurol. Psychiat. 12 (1924), 411.

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EFFECTS OF SINGLE DOSE PROTON IRRADIATION OF NORMAL SKIN AND Vx2 CARCINOMA IN RABBIT EARS

A comparative investigation with protons and roentgen rays

by

Sture Falkmer, Börje Larsson, and *Stig Sténson*

High-energy protons as well as deuterons and alpha particles have unique radiologic properties (WILSON 1946, TOBIAS et coll. 1952). They show a definite range of penetration and the rate of energy loss is many times less at the point at which the protons enter the tissue than in the latter part of their range. The depth dose curve therefore shows a distinct maximum, the 'Bragg peak', in this latter part of the course, provided that the initial energy spread of the particles is relatively small. The scattering of these heavy particles is, at least for the purpose of tumour therapy, almost negligible, and the proton beam is not especially impeded by bony tissue. The maximum biologic efficiency of the secondary radiation is about 1 per cent of that of the beam. High-energy protons are thus physically well-suited for precise irradiation of both deep-seated tumours and superficial tumours adjacent to radiosensitive tissue.

A preliminary report of this investigation was given at the Meeting of the Uppsala Medical Society, May 21st, 1958. Submitted for publication 23 March 1959.

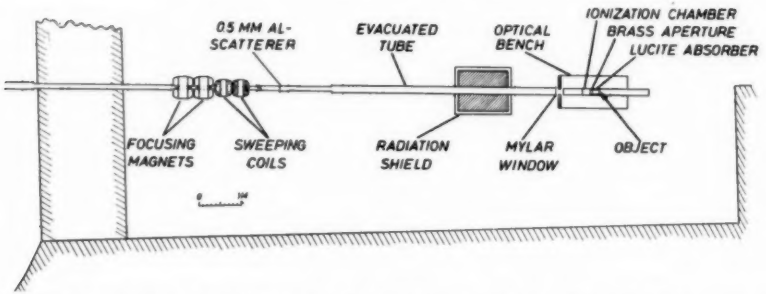

Fig. 1. Plan for irradiation of rabbit skin and Vx2 carcinoma with protons from the synchrocyclotron. The final aperture, ionization chamber and Lucite absorber were aligned on the 'optical bench'. The rabbit ears were centrally fixed to the back of the absorber with adhesive tape. The doses were checked and the beam controlled from a shielded control area.

The biologic effects of protons and deuterons have been studied in Berkeley, Chicago, and Uppsala. Animal experiments have been performed to investigate the effects of irradiation of the pituitary gland (cf. TOBIAS et coll. 1958, VAN DYKE et coll. 1959) and the central nervous system (ANDERSON et coll. 1957, LARSSON et coll. 1958 and 1959) as well as the effects of partial or whole-body irradiation (ROSAHN et coll. 1952, SWIFT et coll. 1955, WARSHAW and OLDFIELD 1957). Only one paper (TOBIAS et coll. 1952) reports the effect of direct irradiation of a malignant tumour, a transplantable mammary carcinoma in the Strong A strain of mice irradiated with deuterons. No histopathologic details, however, were given of the effect of the radiation on the tumour cells.

The present report describes a pre-therapeutical investigation using the 185 MeV proton beam from the 230 cm synchrocyclotron at the Gustaf Werner Institute, Uppsala. It includes a histologic description of the acute effects of single doses of protons in the Bragg peak region on normal rabbit skin and subcutaneously inoculated Vx2 carcinoma. An attempt is also made to make a qualitative and semi-quantitative comparison of the effects of proton irradiation with those produced by conventional roentgen rays.

Irradiation technique

Protons. A brief description of the equipment and the radiologic properties of the 185 MeV proton beam has been given in a previous report (LARSSON et coll. 1956).

The external beam, collimated and focused by two pairs of quadrupole magnets, was brought through an evacuated tube into a shielded room

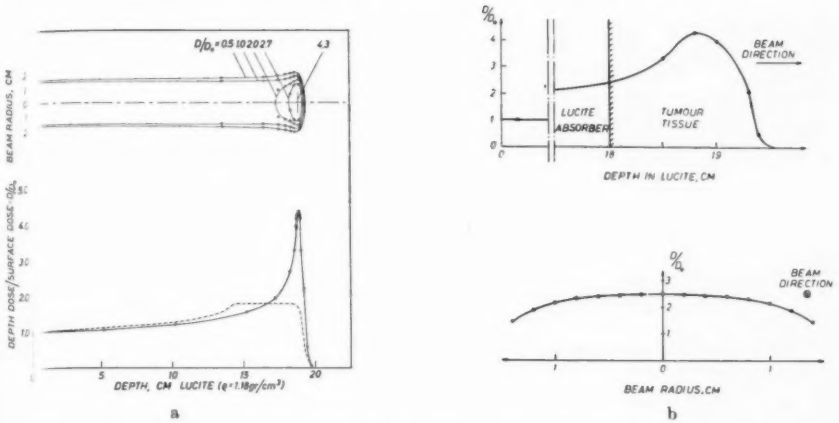

Diagram 1. Dose distributions of a proton beam with an initial diameter of 3 cm. The doses were determined by ionization chambers and photographic film dosimetry. D/D_0 is the ratio depth dose to surface dose. a) The dotted curve in the lower part was obtained by variation of the range of the protons during irradiation. b) Curves showing the longitudinal and transverse dose distributions in the irradiated tumours, measured in the plane of irradiation at a depth of 18.0 cm Lucite.

(Fig. 1) adjoining the cyclotron hall. The strongly non-homogenous cross-section of the beam was smoothed out with a 0.5 mm Al-scatterer, 8 m in front of the target. Before the protons passed through the scatterer, two magnetic coils swept the beam horizontally and vertically. Thus, the beam was made to describe a 6 × 6 cm diamond lattice at the site of irradiation (cf. LARSSON et coll. 1959). The sweep frequencies were 0.7 and 0.6 cycles per second, respectively. The uniformity of the beam cross-section was checked by analysing the C^{11} activity induced in a densely packed mosaic of polystyrene cubes, 6 mm thick. The mean flux density of the proton beam was found to vary about ± 2 per cent in that part of the beam cross-section used for the irradiations. The particles left the evacuated tube through a mylar window (2 mg/cm²) in front of an ionization chamber (600 mg/cm²). The final cross-section of the beam was then determined by a circular aperture, 2 or 3 cm in diameter. Finally, before entering the object to be irradiated, the protons passed through a 17.6 cm Lucite (Perspex) absorber (20.7 g/cm²) which decreased the mean energy of the protons to about 40 MeV. The objects, the external ears, fixed with adhesive tape to the back of the absorber, were thus placed in the Bragg peak region (Diagram 1). The ionization chamber, the aperture, and the object were centered on the beam axis with an 'optical bench' parallel to the beam.

The mean dose rate was 2 000 to 4 000 rad/min. (For convenience,

we have used the following units of dose: for protons the unit rad (1 rad = 100 ergs/g); for roentgen rays r (1 r corresponds to ca 95 ergs/g). The dose appeared in pulses of about 10 microseconds duration, 240 times per second. The dose rate/time function was modulated, however, because of the sweeping of the beam and the beam current variations. The latter were usually less than $\pm$ 10 per cent during each irradiation.

The ionization chamber had plane electrodes, and the collection field, 4 kV/cm, was parallel to the beam. The collection volume was 1.00 cm³ and centered on the axis of the beam. The collecting electrode was double-sided and surrounded by a guard ring, 4 cm wide. Two high voltage electrodes were placed symmetrically on each side of the collecting electrode at a distance of 0.40 cm. The chamber gas was nitrogen at atmospheric pressure, and contained less than 0.01 per cent oxygen and 0.0001 per cent water. The ion current was fed to a 1 μF polystyrene-insulated condenser. The collected charge was determined by measuring the voltage across the condenser with a vibrating reed electrometer. The doses were calculated (cf. BIRGE et coll. 1956) from the charge by assuming full collection efficiency and by use of the values 1.13 for the relative mass stopping power of tissue compared to nitrogen and 34.9 eV for the average energy expended per ion pair formed in the gas (JESSE and SADAUSKIS 1955).

Lucite was used as energy absorber since its stopping power and scattering properties are very similar to those of tissue. The depth dose curve and the isodose curves, shown in Diagrams 1 and 2, were measured in a stack of plane parallel Lucite plates. The depth dose curve was obtained with a second ionization chamber which had its small collecting volume placed on the beam axis at the back of the absorber. The isodose curves were determined from density measurements in photographic films (Kodaline Sheet Film Standard KS 3) placed perpendicularly to the beam at various depths in the Lucite phantom and exposed simultaneously. Films exposed at full energy and developed together with the test films were used for calibration. A dose-density curve was prepared, in addition to a curve showing the sensitivity of the emulsion as a function of the depth; the dose at various points in the phantom was then easily calculated from the assumption that the shape of the dose-density curve is independent of the energy of the protons (TOCHILIN et coll. 1956). Diagram 1 shows the dose distribution in a beam initially 3 cm in diameter and gives the characteristic features of the beam: low scattering and a region with higher dose at the end of the range of penetration. The ratio depth dose to surface dose had a maximum of 4.3. The doses mentioned in the text and tables refer to a depth of 18 cm, the length of the Lucite absorber plus the Lucite equivalent of the ionization chamber. The corresponding depth in tissue would have been 22 cm.

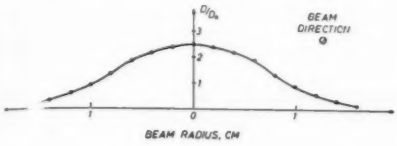

Diagram 2. Transverse dose distribution in the plane of irradiation at a depth of 18.0 cm Lucite of a proton beam with an initial diameter of 2 cm. This beam was used for irradiating the normal rabbit skin.

Roentgen rays. The same apparatus was applied as that routinely used in our department of radiotherapy. The roentgen rays were generated at 220 kV and filtered by 1 mm Al. The dose rate, 500 r/min, was determined by means of an ionization chamber (Philips Type 37480) in the same position as the ears, i. e. fixed to a wooden support, 1.5 cm thick.

Materials and Methods

Female domestic rabbits of a non-inbred native strain were used. They were 5 to 12 months old and weighed 2.6 to 4.0 kg.

Experiments with normal rabbit skin. A total of 54 ears were irradiated with protons, one field of each ear being irradiated. In order to avoid damaging the marginal vessels of the ear with the high doses applied, a proton aperture only 2 cm in diameter was used. The beam cross-section in the plane of the object was about 3 cm (Diagram 2).

Fourteen ears were used in a preliminary series and were irradiated with 640 to 30 000 rad of protons. After irradiation with doses below 2 000 rad, only slight changes were found while doses over 8 000 rad caused complete necrosis. In the main experiment four groups of 10 ears were irradiated with 2 000, 4 000, 6 000, and 8 000 rad, respectively.

For comparison a total of 28 ears in six groups were irradiated with 1 000 to 3 500 r of roentgen rays. The irradiated area was 3 cm in diameter and may be considered uniformly irradiated.

Macroscopic observations of the ears were made once a week. One-third of the animals in each group was sacrificed about 5 weeks and the remainder 26 to 34 weeks after irradiation. The ears were preserved in 10 % formalin and specimens from irradiated and non-irradiated tissue were cut out, embedded in paraffin, and sectioned at 5 to 10 μ. The sections were stained by the van Gieson, Schiff, and toluidine blue methods.

Experiments with Vx2 carcinoma. The strain of Vx2 carcinoma (cf. Dunham and Stewart 1953) used, 'V_2 (Indiana)' (Palmer 1956), was

obtained from Dr. B. Tjernberg of the Department of Obstetrics and Gynaecology, University of Uppsala, who had originally received it from Dr. C. G. Palmer, Indiana University Medical Center Tumour Research Laboratory in 1956. At that time it had been carried in her laboratory for about five years. Dr. Palmer used routine transplants of cell suspensions into the thigh muscles of New Zealand white rabbits. We have now propagated the tumour by that method for more than two years with 100 per cent 'takes' in our rabbits. We have been able to confirm the main statements in the literature (cf. DUNHAM and STEWART 1953) about the biological and histological properties of the tumour.

The experimental tumour was inoculated into the external ear by a modification of the method of WILLIAMS (1951). Only one tumour was implanted into each ear, about 10 mm^3 of the tumour being used instead of 1 mm^3. Sixty per cent 'takes' were obtained. One week after inoculation the tumours had as a rule attained a base diameter of 0.5 cm. The tumours were used in the experiments when they were 9 to 34 days 'old' and had a base diameter of 0.5 to 2.0 cm. Care was taken to allot the tumours evenly as to 'age' and size in the two irradiated groups.

The number of tumours in the two groups were: proton group 91 and roentgen group 60. The irradiations were performed in the same manner as those of 'normal rabbit skin' except that the diameter of the proton beam aperture was 3 cm in order to ensure that all tumour tissue was irradiated. The doses were 500 to 4 000 rad for protons and 500 to 2 000 r for roentgen rays. Diagram 1b shows the proton dose distribution; the roentgen dose may be considered constant in the irradiated tissue, no tumour being more than 1 cm thick.

The rabbits were sacrificed 12 hours to 8 days after irradiation. The ears were fixed in 10 % formalin, and the area of interest was embedded in paraffin and sectioned at 5 to 10 μ. The sections were stained according to the method of van Gieson. When ample amounts of viable-looking tumours were found, only a few meridional sections were studied with the microscope. In all other cases the area where the tumour had been implanted was investigated by serial sections.

Experimental results

Effects on normal rabbit skin

Type of changes. The same type of radiation changes was found in the skin irradiated by protons and roentgen rays. The macroscopic changes were mainly epilation, erythema, desquamation, exudation, and — at higher doses — bullous lesions, ulcerations, and necrosis.

The microscopic alterations are described in the following paragraph.

Semi-quantitative comparison. To compare the effects of protons and roentgen rays on the skin, a macroscopic semi-quantitative grading was made partly by use of the evaluation technique applied to human skin (cf. STRANDQVIST 1944): '*epidermitis erythematosa*', '*epidermitis sicca*', '*epidermitis exsudativa*', and '*epidermitis necroticans*'. In the rabbits used, it was found convenient to detach the feature epilation from this evaluation scheme and to make a semi-quantitative grading of it separately. The grading principles for the epilation are given in Table 1b.

Histologic examination of the radiation-induced cutaneous changes was made as described above. The microscopic assessment conformed essentially with the macroscopic assessment.

'*Epidermitis erythematosa*' in these rabbit ears corresponded histologically to the following features: a slight atrophy of the epidermis with disappearance of most of the rete ridges, atrophy and diminution of the hair follicles and sebaceus glands, and a moderate hyperemia.

In '*epidermitis sicca*' the atrophy of the epidermis, the hair follicles, and the sebaceus glands was marked. Only small remnants of the adnexal structures could be detected, and no hairs were seen. The epithelium was smooth and thin with a complete absence of rete ridges (Fig. 2). In some places, however, the epidermis showed hyperkeratosis and acanthosis. A scanty, inflammatory reaction could sometimes be noted in the superficial parts of the corium.

In '*epidermitis exsudativa*' the essential histologic features were the same as those described for *epidermitis sicca*. The inflammatory reaction was, however, practically always present in the corium, and sometimes subepidermal bullae were observed; moreover, the collagen bundles were often coarse and markedly hyaline. Small remnants of hair follicles were found in some places.

'*Epidermitis necroticans*', lastly, corresponded microscopically to an ulcerated skin with severe damage of the epithelium, connective tissue, and underlying cartilage. The epidermis bordering the ulceration often showed a moderate degree of pseudoepitheliomatous hyperplasia. There were no traces of hair follicles or sebaceus glands. The connective tissue was conspicuously hyaline and sclerotic with thick, densely packed collagen bundles. There were inflammatory changes and destruction of the ear cartilage at the base of the ulcer. No obvious alterations in the vessels could be noted.

The results of the macroscopical assessment of the skin changes after proton and roentgen irradiation are shown in Tables 1a and 1b.

Tables 1 a and 1 b

Semi-quantitative comparison of the effects of protons and roentgen rays on skin (1 d

Experimental group	Dose	Rabbit No.	Epidermitis						
			Weeks after irradiation						
			4—5	7—8	10—11	12—15	16—18	20—21	23—
Rabbit ears irradiated with protons	2 000 rad	134 R	+	+	+	+		0	0
		135 R	0	+	+	+	+	+	0
		136 R	+	+	+	+		0	0
		565 R	+	+	+	+	+	+	0
		618 R	+	+	+	+	+	+	0
	4 000 rad	134 L	++	+	+	+		0	0
		135 L	++	+	+	+	+	+	0
		136 L	++	+	+	+	+	+	0
		565 L	+	++	++	+	+	+	0
		618 L	+	+	++	++		+	0
	6 000 rad	98 R	+	++	++	++	+	+	0
		99 R	0	++	+	+	+	+	+
		100 R	+	++	++	++	+	+	N
		101 R	+	++	++	++	++	++	N
		102 R	0	++	++	++	++	+	+
		103 R	+	++	+	+	+	+	0
	8 000 rad	98 L	+	++	+++	+++	+++	+++	N
		99 L	+	++	++	++	++	++	++
		100 L	++	+++	+++	+++	N	N	N
		101 L	++	+++	N	N	N	N	N
		102 L	++	+++	+++	+++	+++	+++	N
		103 L	++	+++	++	+	+	+	0
Rabbit ears irradiated with roentgen rays	1 000 r	143 R	0	0	0	0	0	0	0
		143 L	0	0	0	0	0	0	0
		144 R	0	0	0	0	0	0	0
		144 L	0	0	0	0	0	0	0
	1 500 r	146 R	0	0	0	0	0	0	0
		147 R	0	+	++	++	++	+	0
		148 R	0	0	0	0	0	0	0
	2 000 r	146 L	0	0	0	0	0	0	0
		147 L	0	+	++	++	++	++	++
		148 L	0	+++	+++	+++	+++	+	+
	2 500 r	166 R	++	+++	+++	+++	N	Rabbit dead	
		166 L	+++	+++	+++	+++	N		
		167 R	++	++	++	++	+++	+++	N
		167 L	++	++	++	++	N	N	N
	3 000 r	168 R	+++	+++	+++	+++	+++	+++	N
		169 R	++	+++	+++	+++	+++	+++	+++
		170 R	++	+++	+++	+++	N	N	N
	3 500 r	168 L	+++	+++	+++	+++	+++	+++	N
		169 L	++	+++	+++	N	N	N	N
		170 L	++	+++	+++	+++	N	N	N

0 no changes.
\+ 'epidermitis erythematosa'.
++ 'epidermitis sicca'.
+++ 'epidermitis exsudativa'.
N 'epidermitis necroticans'.

equals 100 ergs/g, 1 r corresponds to circa 95 ergs/g)

Experimental group	Dose	Rabbit No.	Epilation						
			Weeks after irradiation						
			4—5	7—8	10—11	12—15	16—18	20—21	23—27
Rabbit ears irradiated with protons	2 000 rad	134 R	+	+	+++	+++	++	++	++
		135 R	+	+++	+++	+++	+++	+	0
		136 R	+	+	+++	+++	+++	++	++
		565 R	0	+	+++	+++	++	+	+
		618 R	+	+	++	+++	++	+	+
	4 000 rad	134 L	+	+++	+++	+++	+++	+++	+++
		135 L	+	+	+++	+++	+++	+++	++
		136 L	+	+	+++	+++	+++	+++	++
		565 L	0	++	+++	+++	++	++	++
		618 L	+	++	++	+++	+++	+++	+++
	6 000 rad	98 R	++	++		+++	+++	+++	+++
		99 R	0	+++	+++	+++	+++	+++	++
		100 R	++	+++	+++	+++	+++	+++	N
		101 R	++	+++	+++	+++	+++	+++	N
		102 R	0	+++	+++	+++	+++	+++	++
		103 R	++	+++	+++	+++	+++	+++	++
	8 000 rad	98 L	++	+++		+++	+++	+++	N
		99 L	0	+++	+++	+++	+++	+++	+++
		100 L	++	+++	+++	+++	+++	N	N
		101 L	++	+++	N	N	N	N	N
		102 L	0	+++	+++	+++	+++	+++	N
		103 L	++	+++	+++	+++	+++	+++	++
Rabbit ears irradiated with roentgen rays	1 000 r	143 R	0	0	0	+	++	++	++
		143 L	0	0	0	+	++	++	++
		144 R	0	0	0	0	0	0	0
		144 L	0	0	0	0	0	0	0
	1 500 r	146 R	0	0	0	0	0	0	0
		147 R	0	+	+++	+++	+++	+++	+++
		148 R	0	0	0	0	++	+++	++
	2 000 r	146 L	0	0	0	++	++	++	++
		147 L	0	+	+++	+++	+++	+++	++
		148 L	0	++	++	+++	+++	+	+
	2 500 r	166 R	+	+++	+++	+++	N	Rabbit dead	
		166 L	0	+++	+++	+++	N	»	
		167 R	+++	+++	+++	+++	+++	+++	N
		167 L	0	+++	+++	+++	N	N	N
	3 000 r	168 R	+++	+++	+++	+++	+++	+++	N
		169 R	+	+++	+++	+++	+++	+++	+++
		170 R	+++	+++	+++	+++	N	N	N
	3 500 r	168 L	+++	+++	+++	+++	+++	+++	N
		169 L	+++	+++	+++	N	N	N	N
		170 L	+	+++	+++	+++	N	N	N

0 no epilation.
+ slight epilation.
++ moderate epilation.
+++ total epilation.

In order to save space, the results of observations on the rabbits sacrificed five weeks after irradiation have been omitted in the tables. They confirmed well to the results of observation given in the first columns of Tables 1a and 1b, respectively.

Table 1a shows that the proton dose 4 000 rad evoked '*epidermitis sicca*' with complete healing 23 to 27 weeks after irradiation, while the much lower dose of roentgen rays 2 500 r produced '*epidermitis necroticans*' within 16 weeks after irradiation. '*Epidermitis necroticans*' following proton irradiation was obtained only when the dose amounted to 6 000 rad or more. No necrosis occurred within 27 weeks when the dose of protons was 4 000 rad or less. With roentgen rays, however, severe necrosis was noted following irradiation with 2 500 r.

Table 1b shows that, as regards the single feature epilation, no clear difference was noted between approximately equivalent doses of protons and roentgen rays.

It is thus seen that irradiations with protons in the Bragg peak region of the beam caused less damage to the rabbit skin than irradiations with 220 kV roentgen rays of numerically equivalent doses.

Effects on Vx2 carcinoma

Type of changes. Gross regression of the implanted tumours was noted about two weeks after irradiation with 2 000 rad in the case of protons and 2 000 r in that of roentgen rays. The strain of Vx2 carcinoma used could thus be classified as 'radiosensitive' (WARREN 1944). With the doses mentioned, the irradiated tumours disappeared completely; the non-irradiated control tumours showed progressive growth. No macroscopic difference of the tumour regression was observed following irradiation with approximately equivalent doses of protons or roentgen rays.

Microscopically, too, the same radiation-induced regressive changes were noted in the tumours irradiated by protons as in those irradiated by roentgen rays. The principal changes, all previously recognized (WARREN 1944), were: vacuolization of the cytoplasm, abnormal mitoses, exaggerated cellular and nuclear pleomorphism with the formation of multinucleated giant cells, blurring of the chromatin structure of the nuclei, pyknosis, and necrosis. Ultimately the carcinoma was replaced by connective tissue. The microscopic appearance of the early stages in the tumour cell regression caused by proton irradiation is shown in Fig. 3, b, c and d.

Semi-quantitative comparison. To compare the regressive changes of the Vx2 carcinoma cells following proton and roentgen irradiation, a semi-quantitative grading into four groups was attempted.

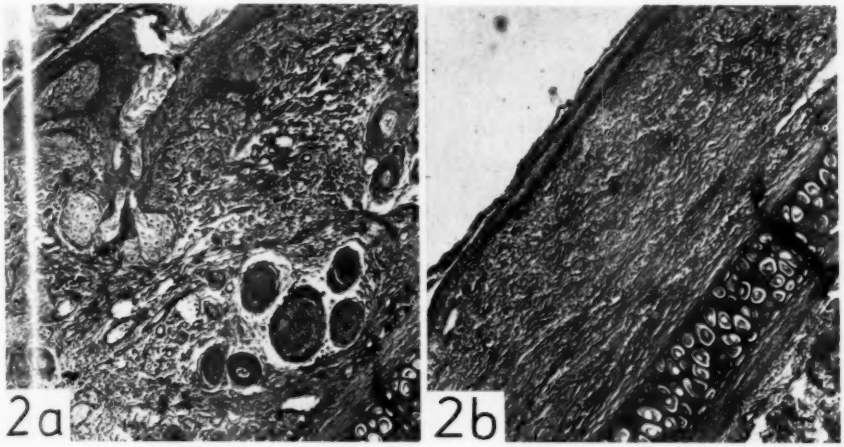

Fig. 2. Microscopic changes in rabbit ear after proton irradiation. (The same types of changes were seen also after roentgen irradiation.) a) Photomicrograph of non-irradiated control, showing the somewhat uneven, fairly broad epidermis with many hair follicles and sebaceus glands in the cellular, loose connective tissue of the corium. The ear cartilage is seen in the lower right corner of the photomicrograph. b) Photomicrograph of an ear irradiated with protons (4 000 rad, observation time 4 weeks), showing '*epidermitis sicca*'. The thickness of the skin is reduced (ear cartilage in the lower right). The epidermis is thin and smooth. The rete ridges, the hair follicles, and the sebaceus glands are absent. The connective tissue of the corium is hyaline and sclerotic. Schiff stain × 120.

Grade c Apparently viable carcinoma without regressive changes in the tumour cells (Fig. 3a).

Grade + Apparently viable carcinoma with slight to moderate regressive changes in the tumour cells, mainly vacuolization of the cytoplasm, some abnormal mitoses and a few multinucleated giant tumour cells (Fig. 3b). Most of the carcinomatous tissue was, however, morphologically intact.

Grade ++ Regressive changes in the tumour cells were marked. Most of the cancer cells were swollen and vacuolated with distorted, intensely hyperchromatic nuclei (Fig. 3c). Multinucleated giant cells of grotesque appearance were numerous. The carcinoma was not split up by connective tissue.

Grade +++ Only sparse remnants of the carcinoma, small nests of tumour cells in newly formed cellular connective tissue, were found (Fig. 3d). The cancer cells showed marked regressive changes similar to those in *grade* ++.

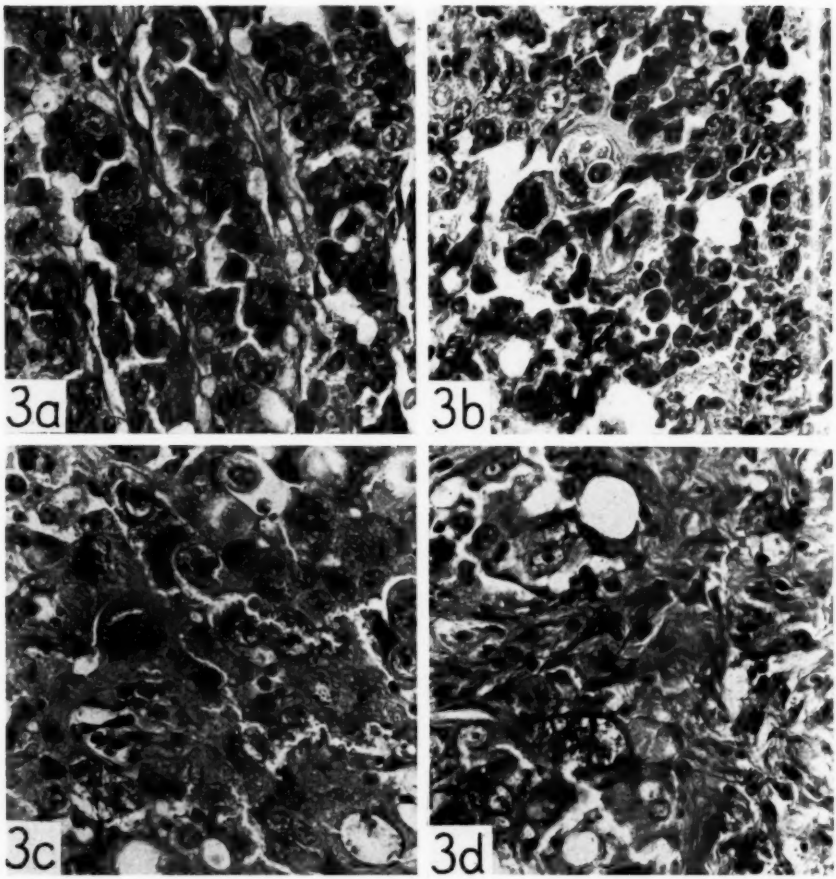

Fig. 3. Photomicrographs showing intact Vx2 carcinoma and three different degrees of tumour cell regression after proton irradiation. (The same type of changes were seen also after roentgen irradiation.)

a) *Grade c* (in Table 2). Non-irradiated carcinoma with solid cords of medium-sized cancer cells, showing only slight pleomorphism and vacuolization.

b) *Grade* + of microscopic tumour cell regression. The pleomorphism of the carcinoma is exaggerated with occurrence of multinucleated giant cells. Several cancer cells show vacuolization of the cytoplasm. Most of the carcinoma is, however, structurally intact. (Proton dose 3 000 rad, observation time 1 day.)

c) *Grade* ++ Practically no structurally intact carcinoma remains. The cancer cells show extreme vacuolization and distorted nuclei with intense hyperchromasia and blurring of the chromatine structure. There is no fibrosis. (Proton dose 3 000 rad, observation time 4 days.)

d) *Grade* +++ The markedly altered carcinoma is being replaced by cellular connective tissue and inflammatory cells, splitting the tumour into small nests of apparently dying cancer cells. (Proton dose 3 000 rad, observation time 8 days.)

van Gieson stain × 480.

Table 2

Semi-quantitative comparison of the ability of protons and roentgen rays to cause microscopic regressive changes in Vx2 carcinoma. Each marking gives the result of observation of one tumour.

Experimental group	Dose	Time (in days) after irradiation					
		0.5	1	2	4	6	8
Tumours irradiated with protons	500 rad	c	c	+	+	++	++
		c		+	+	+	++
				c			
	800 rad	c	+	c	+	++	+
				c	+	+	+
	1 000 rad	c	+	+	++	++	++
			c		+	++	
	1 200 rad	c	c	c	++	++	++
		c	c			++	+
							+
	1 500 rad	c	c	+	++	++	++
		c	+		++	++	+
						+++	++
	2 000 rad	c	c	+	++	++	++
			c	c	+	++	+++
				+	++	++	+++
					+		+++
	3 000 rad	+	+	++	+++	+++	+++
		c	+		++	++	
	4 000 rad	c	c	++	+	++	+++
					+++	+++	+++
Tumours irradiated with roentgen rays	500 r	c	+	+	+	+	+
			+	c			+
	800 r	c	+	+	+	+	c
		+	+	+		+	++
				+		++	
	1 000 r	c	c	+	++	c	+
						+	
	1 200 r	c	c	c	+	+	+
		c	c	+	+	+++	c
							++
	1 500 r	c	c	++	++	++	+
					+	+++	+++
	2 000 r	c	c	++	+++	++	+++
			c			++	+++

c signifies intact, viable carcinoma. (Fig. 3 a.)

\+ " slight to moderate regressive changes in part of the carcinoma. (Fig. 3 b.)

++ signifies severe regressive changes in most of the cancer cells but without replacement by connective tissue. (Fig. 3 c.)

+++ signifies severe regressive changes with early replacement of the carcinoma by connective tissue. (Fig. 3 d.)

The amount of necrosis in the tumours was not included in this grading because the Vx2 carcinoma in itself readily becomes necrotic (cf. DUNHAM and STEWART 1953), and, consequently, it could not be determined whether a necrotic area was induced by irradiation or not.

All the microscopic sections were examined as unknowns. The final grading of the section was the result of at least three reviews of the entire material. The gradings on different occasions agreed well with each other.

The occurrence of the different degrees of microscopic tumour cell regression in the two experimental groups after various doses and different times of observation is shown in Table 2. When more than one tumour having had the same radiation dose and observation time was studied, the individual grades of regression are listed under each other in the appropriate part of the table.

Our observations suggest that following the application of approximately equivalent doses of roentgen rays and protons in the Bragg peak region, similar histologic changes occur in the Vx2 carcinoma.

Discussion

The purpose of this investigation was an attempt to learn whether the histologic and biologic effects of the proton beam on normal tissue and on a radiosensitive carcinoma would be similar to those of roentgen rays. The experiments were also planned in order to obtain semi-quantitative information about these effects.

The Bragg peak region was chosen because this part of the beam presumably would be used if protons were applied to the radiotherapy of malignant tumours (*vide* infra).

The skin was used both because it is radiosensitive and readily accessible, and also because changes in it are easy to observe and assess semi-quantitatively. The choice of rabbit ear skin allowed the proton and roentgen dose distributions to be made rather similar.

When the experimental animals with suitable malignant tumours were chosen for these experiments, the principles given by TOBIAS et coll. (1952) were followed: the size of the tumour at the time of irradiation should be small compared to the size of the animal. It should be possible to irradiate the tumour without irradiating at the same time too large a part of the body. The extent of the tumour should be easily established in order to ascertain that all tumour tissue was irradiated. The tumours should not metastasize early from the site of implantation. These conditions were fulfilled by the choice of rabbits with Vx2 carcinoma implanted subcutaneously in the external ears. The late spontaneous

regression of this tumour when implanted in the ears (WILLIAMS 1951) is not a drawback, since, in the present investigation, only the short-time effects were studied.

Vx2 carcinoma, a malignant transformation of the Shope papilloma, was originally a virus-induced tumour (KIDD and ROUS 1940), but in 1952 the Vx2 carcinoma was shown to have lost its ability to stimulate any resistance to the Shope virus, and complement-fixing antibodies against the papilloma virus could not be demonstrated (ROUS et coll. 1952, GINDER and FRIEDEWALD 1952). The strain 'V_2 (Indiana)' used has a somewhat higher mean chromosome number than the original Vx2 carcinoma (PALMER 1956), otherwise there are no known differences in the two strains. Histologically it may be characterized as an anaplastic necrotizing epidermoid carcinoma. It might thus be expected that the Vx2 carcinoma would be rather radiosensitive, as demonstrated in our experiments.

WILLIAMS (1951) stated that Vx2 carcinoma implanted subcutaneously into the external ear showed progressive growth up to nearly six months after inoculation. The overlying skin began to ulcerate about six weeks after the implantation. The tumours were said never to form metastases and in no case caused death of the animals. The fact that the carcinomata implanted into the ears showed quite a different biologic course from those implanted into the leg muscles (where they showed progressive growth, early metastases, and killed the animal within 6 to 10 weeks) was ascribed to concomitant inflammatory changes rather than to restricted space for growth, poor blood supply, or low temperature.

In the present experiments WILLIAMS' statements were confirmed although in two rabbits metastases was found in a cervical lymph node six weeks after implanting a tumour into the base of the ear.

There is much evidence to suggest that ionizing electromagnetic radiation, beta- and alpha-radiation, and neutrons cause the same kinds of histologic changes in tissues (cf. WARREN 1944). The different microscopic distributions of the energy transferred to the irradiated tissue seem to have only a quantitative significance for the final effect. As might be expected, the protons used in these experiments do not violate this rule. No qualitative differences between the histologic effects of protons and roentgen rays were observed.

The results given in Tables 1a and 1b show that the protons in the plane of irradiation, with an average energy of 40 MeV, cause less damage to rabbit skin than approximately equivalent doses of 220 kV roentgen rays. The result might be expected to hold also for protons of higher energy, with lower specific ionization.

From Table 2 it may be concluded that single doses of protons in the Bragg peak region cause regressive changes in a radiosensitive

carcinoma with approximately the same efficiency as single doses of 220 kV roentgen rays if all parts of the tumour are given a dose which is not less than the corresponding roentgen dose.

The relative biologic efficiency (RBE) of protons for producing chromosome aberrations in *Allium* and *Vicia* was investigated by LARSSON and KIHLMAN. They give 0.7 as a probable value for the RBE of high energy protons (170 MeV) as compared with 180 kV roentgen rays. This conforms with the fact that the protons damaged the skin less than the roentgen rays. For lower energies, i. e. towards the end of the Bragg peak, they noted a significant increase of the RBE. Further, as the doses given refer to the surface of the tumours, part of the tumour tissue irradiated with protons had received an actual dose higher than the nominal dose (cf. Diagram 1b). These two facts may explain why the protons damaged the skin less than the roentgen rays but caused approximately the same regression of the Vx2 tumour as numerically equivalent roentgen doses.

These findings support the view that the proton beam with its advantageous physical properties may be used in the treatment of malignant tumours. Before the proton beam can be applied to deep-seated tumours, one must assess, however, the radiosensitivity of other intervening tissues. An investigation is in progress to survey the reactions of other organs to varying doses of proton radiation.

The depth dose curve used in these experiments has a peak that is, as a rule, too narrow to permit uniform irradiation of tumours found in man. This limitation can be overcome by a continuous variation of the range during irradiation by means of a variable absorber. By selecting an appropriate sweep function, i. e. thickness of absorber as a function of charge collected from the ionization chamber, it has been possible to adjust the width of the Bragg peak to the size of the tumour to be irradiated. This transformation of the Bragg peak has to be made at the expense of the ratio depth dose/surface dose. One depth dose curve obtained with a remotely controlled water absorber is shown as an example in Diagram 1a. It is the result of an attempt to fit the Bragg peak for uniform irradiation of a 5 cm thick tissue volume.

Acknowledgements

This investigation was initiated by Prof. John Naeslund, who continuously followed the experiments and gave us valuable constructive criticism. Prof. The Svedberg and Prof. Gösta T. Hultquist showed great interest in the work and made available the facilities of their laboratories. Associate Prof. Bengt A. Nohrman, Director of the Department of Radiotherapy, performed the roentgen irradiations and gave us helpful advice throughout the course of the investigation. We wish to express our gratitude for all this kind support.

Thanks are also due to Åke Svanheden and his cyclotron crew for providing an excellent proton beam. The investigation was supported by grants from the Swedish Cancer Society and the Technical Research Council.

SUMMARY

Normal rabbit skin and subcutaneously implanted Vx2 carcinoma were irradiated with protons from a synchrocyclotron, the Bragg peak region of the proton beam being used. The effect was compared with that of 220 kV roentgen rays. Qualitatively the regressive changes were the same. Semi-quantitative grading of the radiation-induced gross changes of the skin showed that protons produced less damage than approximately equivalent doses of roentgen rays. Semi-quantitative grading was also applied to the microscopic regressive changes evoked in the Vx2 carcinoma cells during the first week after irradiation. The proton beam had approximately the same ability as conventional roentgen rays to produce early regressive changes at roughly corresponding doses. The findings give biological support to the idea that the proton beam, with its advantageous physical properties, may be used to treat malignant tumours.

ZUSAMMENFASSUNG

Normale Kaninchenhaut und subkutan darin implantierte Vx2-Karzinome sind mit Protonen eines Synchrocyclotrons bestrahlt worden, wobei die Braggspitzenregion des Protonstrahles benutzt wurde. Der Effekt wurde mit dem von 220 kV-Röntgenstrahlen verglichen. Qualitativ fand man die gleichen regressiven Veränderungen. Semi-quantitative Gradierung der strahleninduzierten makroskopischen Hautveränderungen zeigten, dass die Protonen weniger Schaden anstellten als ungefähr equivalente Röntgendosen. Semi-quantitative Gradierung wurde auch für die Beurteilung der mikroskopischen regressiven Veränderungen benutzt, welche in den Vx2-Karzinomzellen während der ersten Woche nach der Bestrahlung auftraten. Der Protonenstrahl hatte ungefähr das gleiche Vermögen wie die konventionellen Röntgenstrahlen, frühe regressive Veränderungen bei grob gerechnet entsprechender Dosierung zu erzeugen. Die Befunde unterstützten biologisch die Ansicht, dass der Protonenstrahl mit seinen vorteilhaften fysikalischen Eigenschaften für Behandlung maligner Tumoren benutzt werden kann.

RÉSUMÉ

Les auteurs ont irradié avec les protons émis par un synchrocyclotron, en utilisant la région du maximum de Bragg du faisceau de protons, la peau normale de lapins et des greffes sous-cutanées de cancer Vx2. Ils ont comparé l'effet des protons avec celui de rayons roentgen de 220 kV. Qualitativement les modifications régressives ont été les mêmes. Un classement semi-quantitatif des lésions cutanées macroscopiques dues aux radiations montre que les protons ont causé des lésions moins graves que des doses approximativement équivalentes de rayons roentgen. Les auteurs ont aussi appliqué un classement semi-quantitatif aux modifications régressives microscopiques des cellules du cancer Vx2 au cours de la première semaine suivant l'irradiation. A doses à peu près équivalentes, le faisceau protonique et les rayons roentgen usuels produisent approximativement les mêmes modifications régressives précoces. Ces résultats fournissent un argument biologique à l'appui de l'idée que le faisceau protonique, doué de propriétés physiques favorables, peut être utilisé pour le traitement de tumeurs malignes.

REFERENCES

ANDERSON, A., GARCIA, J., HENRY, J. et coll.: Pituitary and hypothalamic lesions produced by high-energy deuterons and protons. Rad. Res. 7 (1957), 299.

BIRGE, A. C., ANGER, H. O. and TOBIAS, C. A.: Heavy charged-particle beams. *In:* H XE, G. J. and BROWNELL, G. L.: Radiation dosimetry, pp. 623—665. New York: Academic Press 1956.

DUNHAM, L. J. and STEWART, H. L.: A survey of transplantable and transmissible animal tumours. J. nat. Cancer Inst. 13 (1953), 1299.

GINDER, D. R. and FRIEDEWALD, W. F.: V_2 carcinoma in the rabbit eye. Cancer Res. 12 (1952), 429.

JESSE, W. P. and SADAUSKIS, J.: Ionization in pure gases and the average energy to make an ion pair for alpha and beta particles. Phys. Rev. 97 (1955), 1668.

KIDD, J. G. and ROUS, P.: A transplantable rabbit carcinoma originating in a virus-induced papilloma and containing the virus in masked or altered form. J. exp. Med. 71 (1940), 813.

LARSSON, B. and KIHLMAN, B. A.: Chromosome aberrations following irradiation with high-energy protons and their secondary radiation. Int. J. Rad. Biol. (In press.)

— LEKSELL, L., REXED, B. and SOURANDER, P.: Effect of high energy protons on the spinal cord. Acta radiol. 51 (1959), 52.

— — — et coll.: The high energy proton beam as a neurosurgical tool. Nature 182 (1958), 1222.

— SVEDBERG, T. and TYRÉN, H.: Djupterapi med protoner vid Uppsalasynkrocyklotronen. (Swedish.) Årsbok för Riksföreningen för kräftsjukdomarnas bekämpande (Yearbook for the Swedish Cancer Society). 1952—1956, pp. 41—46. Stockholm 1956.

PALMER, C. G.: Transplant. Bull. 3 (1956), 14.

ROSAHN, P. D., TOBIAS, C. A. and LAWRENCE, J. H.: Effects on the white mouse of a single whole-body exposure to 190 MeV deuterons. Amer. J. Path. 28 (1952), 37.

ROUS, P., KIDD, J. G. and SMITH, W. E.: Experiments on the cause of the rabbit carcinomas derived from virus-induced papillomas. II. Loss by the Vx2 carcinoma of the power to immunize hosts against the papilloma virus. J. exp. Med. 96 (1952), 159.

STRANDQVIST, M.: Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- und Lippenkarzinomen. Acta radiol. (1944) Suppl. No. 55.

SWIFT, M. N., BOND, V. P., TAKETA, S. T. et coll.: Partial body irradiation of the rat with 190 MeV deuterons. Amer. J. Roentgenol. 73 (1955), 294.

TOBIAS, C. A., ANGER, H. O. and LAWRENCE, J. H.: Radiological use of high energy deuterons and alpha particles. Amer. J. Roentgenol. 67 (1952), 1.

— LAWRENCE, J. H., BORN, J. L. et coll.: Pituitary irradiation with high-energy proton beams. A preliminary report. Cancer Res. 18 (1958), 121.

TOCHILIN, E., SHUMWAY, B. W. and KOHLER, G. D.: Response of photographic emulsions by charged particles and neutrons. Rad. Res. 4 (1956), 467.

VAN DYKE, D. C., SIMPSON, M. E., KONEFF, A. A. and TOBIAS, C. A.: Long term effects of deuteron irradiation of the rat pituitary. Endocrinology 64 (1959), 240.

WARREN, S.: The histopathology of radiation lesions. Physiol. Rev. 24 (1944), 225.

WARSHAW, S. D. and OLDFIELD, D. G.: Pretherapeutic studies with the Chicago synchrocyclotron. Amer. J. Roentgenol. 78 (1957), 876.

WILLIAMS, R. G.: The vascularity of normal and neoplastic grafts in vivo. Cancer Res. 11 (1951), 139.

WILSON, R. R.: Radiological use of fast protons. Radiology 47 (1946), 487.

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BONE MARROW TRANSPLANTATION AND CHEMICAL PROTECTION IN THE RADIOTHERAPY OF MOUSE LEUKEMIA

(Preliminary communication)

by

Emanuel E. Schwartz

Measures that increase tolerance to radiation constitute a potential means of enhancing tumor therapy. HOLLCROFT and MATTHEWS (1953) were the first to report the use of bone marrow transplantation in roentgen treatment of mammalian lymphomas. BARNES et coll. (1956, 1957) and TRENTIN (1957) also showed the possible usefulness of this procedure in radiotherapy of generalized murine leukemia. On the clinical level, THOMAS et coll. (1957) attempted to replenish the marrow of leukemic patients treated with roentgen rays and chemicals by transplanting normal marrow cells. STRAUBE et coll. (1950) observed that intravenous administration of cysteine to rats partially protected the mammary tumors as well as the hosts; hence it did not significantly improve the results of whole-body roentgen irradiation. Similarly, DOMSHLAK et coll. (1957) injected sarcomatous rats with cysteine and sodium cyanide before local irradiation without increasing cure rates despite the fact that the pretreated rats seemed to tolerate roentgen rays better than the controls.

Presented in part at the Meeting of the American Association for Cancer Research, April 1958. Submitted for publication 27 February 1959.

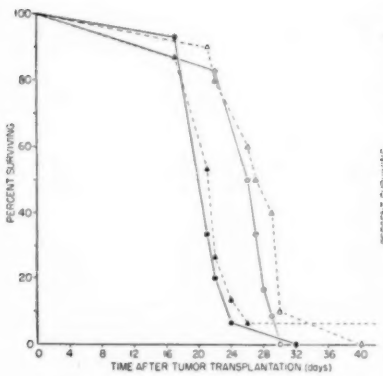

Diagram 1. Effects of AET and bone marrow on survival of irradiated lymphoma-bearing AKR mice. Each group contained 11 to 15 mice. Irradiation was carried out at 98 r/min. △ 700 r followed by bone marrow (1 radiation death excluded); ○, 700 r preceded by AET orally (1 radiation death excluded; ▲, 400 r without other treatment; ● no irradiation, AET, or bone marrow.

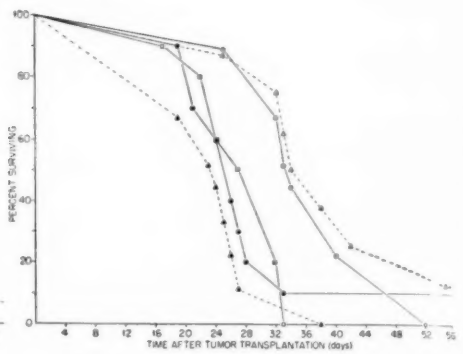

Diagram 2. Effects of AET and bone marrow on survival of irradiated lymphoma-bearing (C3H X 101)F_1 mice. Each group contained 10 mice. Irradiation was carried out at 98 r/min. △, 1 500 r preceded by AET intraperitoneally and followed by bone marrow (excluding 2 radiation deaths); □, 900 r preceded by AET intraperitoneally; ○, 900 r followed by bone marrow (1 radiation death excluded); ▲, 630 r without other treatment (1 radiation death excluded); ●, no irradiation, AET, or bone marrow.

We undertook the present study to further explore the potentialities of these adjuncts to radiotherapy, specifically in relation to 2 transferable, spontaneously arising mouse lymphoid leukemias. Our major objectives were: (1) to compare the efficiency of fractionated and protracted roentgen irradiation with that of single short treatments when both types are combined with bone marrow transplantation, and (2) to explore the value of the chemical protective agent aminoethylisothiuronium · Br · HBr (AET) in radiotherapy.

Methods

Transplantation of lymphomas. The neoplasms used in this study were 2 lymphomas that arose spontaneously in AKR and (C3H X 101)F_1 mice and were maintained by serial transplantation in mice of the strains of origin. Saline suspensions of minced lymphomatous tissues were inoculated subcutaneously into 8- to 9-week-old recipients. The AKR lymphoma was uniformly lethal within several weeks after implantation. The hybrid lymphoma, however, grew progressively in 90 to 100 % of the recipients; one subline killed in 3 to 5 weeks and the other in 2 to 4 weeks after inoculation.

Techniques of irradiation. Mice were irradiated on the day after implantation of the lymphoma. They were exposed in separate compartments of a lucite cage rotating at 7 rpm. Physical factors of the irradiation were: 250 kV, 3 mm of Al filtration (Be

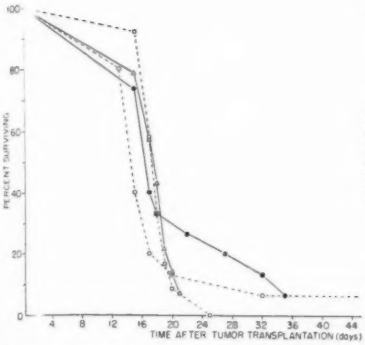

Diagram 3. Effects of orally administered AET on survival of irradiated lymphoma-bearing (C3H X 101)F_1 mice. Treatment groups consisted of 14 to 16 mice. Irradiation was carried out at 98 r/min. □, 800 r preceded by AET orally (2 radiation deaths excluded); △, 550 r without other treatment (2 radiation deaths excluded); ○, AET without irradiation; ●, no irradiation or AET.

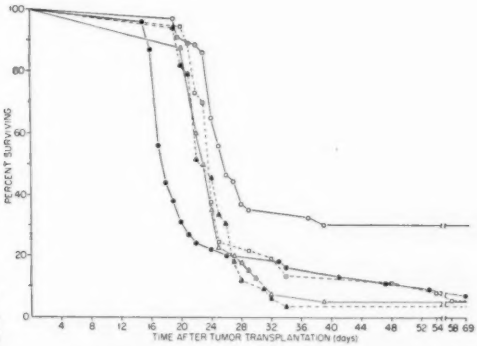

Diagram 4. Effects of fractionation or protraction of irradiation in conjunction with bone marrow transplantation on survival of lymphoma-bearing (C3H X 101)F_1 mice. Each group contained 45 to 46 mice. ▲, 300 r (98 r/min) daily for 5 days, followed by bone marrow after last exposure (13 radiation deaths excluded); □, 650 r (98 r/min) once weekly for 2 weeks, bone marrow after each exposure (9 radiation deaths excluded); ○, 825 r (98 r/min) followed by bone marrow (2 radiation deaths excluded); ▲, 1 300 r (0.8—0.9 r/min) in 25 hours, followed by bone marrow (6 radiation deaths excluded); ●, no irradiation or bone marrow.

window), HVL 0.44 mm of Cu; one set of exposures was given at 98 r/min, 30 mA, and TSD 82 cm; another was given at 0.8 to 0.9 r/min, 360 μA, and TSD 100 cm. At the lower current, constant output was facilitated by incorporation of a current stabilizer in the 250-kV G. E. Maxitron X-ray machine. The dose rate was checked by exposing a 2 500-r Victoreen thimble ionization chamber throughout each treatment and by calibration with a 100-r chamber at the beginning and end of each run.

Administration of bone marrow. Suspensions of isologous bone marrow cells in Tyrode's solution, prepared as described by URSO and CONGDON (1957), were injected into the tail vein within 3 to 5 hours after exposure. One femur-equivalent of marrow (about 12.5 million nucleated cells) was injected into each recipient.

Administration of AET. AET buffered to pH 7.45 was fed by stomach tube (500 or 600 mg/kg) 20 to 30 minutes before irradiation or was injected intraperitoneally (300 mg/kg) in aqueous solution 10 to 40 minutes before irradiation. Under the rapid alkalinization conditions used in these experiments, most of the AET was converted to the mercaptoethylguanidine form before injection (SHAPIRA et coll. 1957).

Results

Mice enabled by bone marrow injection to survive otherwise supralethal roentgen doses lived longer after implantation of lymphoma cells than those given near-lethal roentgen doses without bone marrow or

than the nonirradiated controls (Diagrams 1 and 2). Survival of mice protected by AET against supralethal roentgen doses differed according to strain, being prolonged in AKR mice (Diagram 1) beyond the extent obtained with roentgen rays alone but not in (C3H X 101)F_1 mice (Diagrams 2 and 3). The prolongation given by a single brief supralethal roentgen exposure was not enhanced by fractionation of the dose or by reduction of the dose rate (Diagram 4). The percentage of mice surviving indefinitely, or 'cured' was not significantly affected by any of these treatments. Administration of AET or bone marrow without irradiation did not influence the course of the disease.

Discussion

The longer survival of bone marrow-injected mice, as compared to noninjected, irradiated controls, is attributable in part to the higher doses of roentgen rays tolerated since both treatment groups received maximum sublethal amounts of radiation ($\sim LD_{10}/30$ days). These results confirm earlier observations (HOLLCROFT and MATTHEWS 1953, BARNES et coll. 1956 and 1957, TRENTIN 1957) and further demonstrate the value of bone marrow transplantation in the radiotherapy of leukemia.

The effects of AET are difficult to interpret because of their inconsistency. The enhanced survival of AET-pretreated AKR mice suggests that the lymphoma cells in these mice were not so well protected as normal tissues. This result is in keeping with the relatively poor uptake of orally administered S^{35}-labeled AET by subcutaneous collections of lymphoma cells as compared to the uptake by normal cells of the blood-forming tissues and intestine (E. E. SCHWARTZ, R. SHAPIRA, and D. G. DOHERTY, unpublished data). This observation is also consistent with the findings of others that ascites and other tumor cells may be less well protected by AET against roentgen rays (A. D. CONGER 1957, unpublished data) and nitrogen mustard (KELLY et coll. 1958) than are normal cells. The contrasting failure of AET to similarly increase the survival of irradiated lymphomatous (C3H X 101)F_1 mice warrants further investigation.

Failure of increased amounts of radiation to effect permanent regression of the lymphomas is not surprising, since transplantation assays showed that cells of these neoplasms survived in vivo after doses up to and exceeding 1 500 r in a single treatment (98 r/min). 'Cures' of the type reported by TRENTIN (1957) are probably limited, therefore, to the relatively radiosensitive leukemias.

It is interesting that neither fractionation nor protraction of the radiation dose improved the effects of radiotherapy, even under conditions where radiation mortality was greater than 10 %. In view of earlier

observations that the effectiveness of radiation may be increased by fractionation or protraction (DU SAULT 1956, BARNES et coll. 1956). A further systematic study of time-intensity factors in a variety of tumor-host relations is indicated.

Acknowledgments

I am indebted to Drs. A. C. Upton and C. C. Congdon for providing the transplantable leukemias and for their counsel in the preparation of this study. Thanks are also due to Mrs. Frances F. Wolff and Mr. William Guide for technical assistance and to Drs. R. Shapira and D. G. Doherty for preparation of the AET.

SUMMARY

Attempts were made to extend the radiation-induced survival of mice, bearing transplanted lymphomas, by the use of isologous bone marrow or the radioprotective chemical AET. Increased amounts of radiation tolerated by virtue of post-treatment with isologous bone marrow prolonged survival beyond that obtainable with sublethal doses of roentgen rays alone. Increased amounts of radiation tolerated by virtue of pre-treatment with AET also further prolonged survival in one of the 2 transplanted lymphomas studied, which suggests that in this instance normal tissues received greater protection than the lymphoma. Fractionated or protracted irradiation was not significantly more effective than a single brief exposure under the conditions tested.

ZUSAMMENFASSUNG

Versuche wurden angestellt, die strahleninduzierte Überlebenszeit von Mäusen mit transplantierten Lymphomen durch Benutzung von isologem Knochenmark oder des chemischen Strahlenschutzmittels AET zu verlängern. Grössere Strahlenmengen, welche mit Hilfe von Behandlung mit isologem Knochenmark nach der Bestrahlung vertragen wurden, verlängerten die Überlebenszeit über diejenige hinaus, welche mit subletalen Röntgendosen allein erzielt werden kann. Grössere Strahlendosen, welche durch die Vorbehandlung mit AET vertragen wurden, verlängerten weiterhin in einem von den beiden studierten transplantierten Lymphomen die Überlebenszeit. Letzteres deutet an, dass in diesem Falle das normale Gewebe besser geschützt war als das Lymphom.

RÉSUMÉ

Sur des souris porteuses de lymphome greffé, l'auteur a essayé d'allonger, grâce à la moëlle osseuse isologue ou au radioprotecteur chimique AET, le temps de survie obtenu par irradiation. Les doses d'irradiation plus fortes tolérées grâce au post-traitement par la moëlle osseuse isologue ont donné une survie plus longue que celle qu'on peut obtenir par des doses subléthales de rayons roentgen seules. Les doses d'irradiation plus fortes tolérées grâce au pré-traitement par l'AET ont aussi prolongé la survie dans un des deux cas de lymphome greffé étudiés; ceci fait penser que dans ce cas les tissus normaux ont bénéficié d'une protection plus importante que le lymphome.

REFERENCES

Barnes, D. W. H., Corp, M. J., Loutit, J. F. and Neal, F. E.: Treatment of murine leukaemia with X-rays and homologous bone marrow (Prelim. Com.). Brit. med J. 1956: II, p. 626.

— and Loutit, J. F.: Treatment of murine leukaemia with X-rays and homologous bone marrow: II. Brit. J. Haemat. 3 (1957), 241.

Domshlak, M. P., Ivanov, I. I., Belovsow, O. I. and Jakowlew, W. G.: Biological protection against radiation in experimental X-ray therapy of tumours. Med. radiol. 2 (1957), 47.

Du Sault, L. A.: Time-dose relationships. Amer. J. Roentgenol. 75 (1956), 597.

Hollcroft, J. W. and Matthews, M.: Effects of ionizing irradiation treatments on tumor regression. J. nat. Cancer Inst. 14 (1953), 527.

Kelly, M. G., O'Gara, R. V., Rall, D. P. and Zubrod, C. G.: Effect of S,2-aminoethylisothiuronium bromide hydrobromide (AET) on the toxicity and antitumor activity of "radiomimetic" drugs. Proc. Amer. Ass. Cancer Res. 2 (1958), 313.

Shapira, R., Doherty, D. G. and Burnett, Jr., W. T.: Chemical protection against ionizing radiation. III. Mercaptoalkylguanidines and related isothiuronium compounds with protective activity. Radiat. Res. 7 (1957), 22.

Straube, R. L., Patt, H. M., Smith, D. E. and Tyree, E. B.: Influence of cysteine on the radiosensitivity of Walker rat carcinoma 256. Proc. Amer. Ass. Cancer Res. 10 (1950), 243.

Thomas, E. Donnall, Lochte, Jr., H. L., Lu, W. C. and Ferrebee, J. W.: Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. New Engl. J. Med. 257 (1957), 491.

Trentin, J. J.: Whole-body X-ray and bone marrow therapy of leukemia in mice. Proc. Amer. Ass. Cancer Res. 2 (1957), 256.

Urso, P. and Congdon, C. C.: The effect of the amount of isologous bone marrow injected on the recovery of hematopoietic organs, survival, and body weight after lethal irradiation injury in mice. Blood 12 (1957), 251.

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QUALITY AND CHOICE OF POTTER BUCKY GRIDS

III. The choice of a Bucky grid

by

J. G. Bonenkamp and *W. Hondius Boldingh*

It was shown in P. II, heading (1), that the lead content is a better measure of the quality of a Bucky grid than the ratio. In order to gain deeper knowledge of this subject it is necessary to calculate the transmission of the primary and of the scattered radiation as a function of the quantities determining the construction of the grid. For this purpose we shall use the following symbols (see Fig. 1):

μ (cm^{-1}) the effective absorption-coefficient of the interspacing, which is dependent on voltage and phantom thickness

d (cm) the thickness of the lead lamellae

D (cm) the distance of the lead lamellae

h (cm) the height of the lead lamellae

The geometrical dimensions of the grid are determined from these data, and hence the grid quantities which are of immediate practical importance, viz.:

$$n \text{ (cm}^{-1}\text{)} = \text{number of lamellae per cm} = \frac{1}{d + D} \quad (1)$$

$$r = \text{ratio} = \frac{h}{D} \quad (2)$$

$$P \text{ (cm}^3/\text{cm}^2\text{)} = \text{lead content per cm}^2 = n \cdot d \cdot h \quad (3)$$

Submitted for publication 22 December 1958.

We shall now with the aid of these quantities formulate the transmission of primary and scattered radiation and thus ascertain their mutual interdependence.

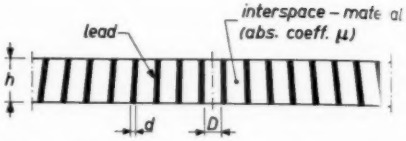

Fig. 1. Symbols used in the grid calculations.

1. Optimum transmission of the primary radiation

The part covered by lead per cm² of grid surface is equal to $n \cdot d = P/h$. For a specific value of P therefore, that part is small when h is great: we assume that the lead absorbs all incident rays and that as a result of a correct centering of the lamellae to the focus the rest of the primary radiation, i. e. $1-P/h$ per cm², does not strike the lead.

In the interspacing this part undergoes attenuation with a factor $e^{-\mu h}$. For a specific value of μ this attenuation is small when h is small.

The transmission of the primary rays is now

$$Tp = (1 - P/h)\ e^{-\mu h} \tag{4}$$

and is thus determined by two mutually opposed functions of h.

For a given lead content P and a given interspacing material μ it will be possible to find an optimum value of h for which the transmission Tp has a maximum value. Upon differentiation we get:

$$\frac{dTp}{dh} = (-\mu + \frac{\mu P}{h} + \frac{P}{h^2})e^{-\mu h} = o, \text{ thus } -\mu + \frac{\mu P}{h} + \frac{P}{h^2} = o.$$

This quadratic equation gives one acceptable solution, viz.

$$h = \tfrac{1}{2}\ P\ (1 + \sqrt{1 + \frac{4}{\mu P}}) = h_{opt}. \tag{5}$$

As μ generally is $\leqslant 0.3$ (organic interspacing) and $P < 0.1$ (see Table 1 in part II), and therefore $\mu P < 0.03 \ll 4$ we may write as a first approximation $h_{opt} = \sqrt{\frac{P}{\mu}}$.

With this value of h and with a given absorption of the scattered radiation, the maximum transmission of the primary rays reaches the value

$$Tp = \left(1 - \sqrt{\mu P}\right) e^{-\sqrt{\mu P}}$$

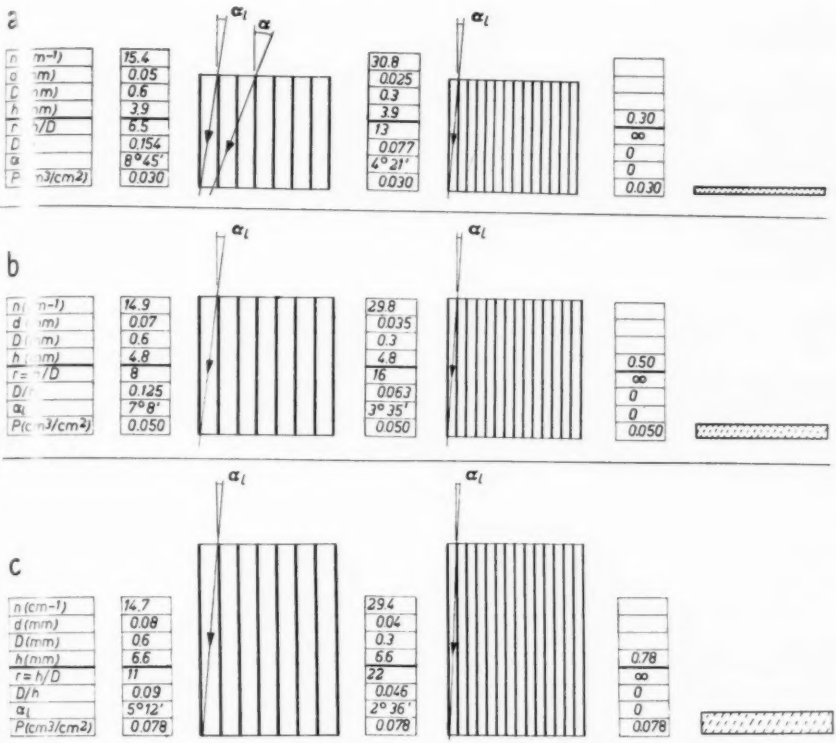

Diagram 1. Three groups: a, b and c, of three grids with lead contents of 0.30, 0.50 and 0.078, respectively. In each group the second grid, in comparison with the first, contains twice as many lamellae per cm but on half their thickness. The ratio is thus doubled with conservation of the lead content. The third 'grid' type in each group is a lead plate ($r = \infty$) with the same lead content.

This formula means that for this optimum case. the absorption of the primary radiation by the lead is about equal to that by the interspacing: $Tp \approx \left(1 - \sqrt{\mu P}\right)^2 \approx e^{-2\sqrt{\mu P}}$

2. Transmission of the scattered radiation

The quantity of scattered radiation transmitted by a grid depends on the lead content and the ratio. For a correct calculation of the transmission, the relative intensity and quality of the scattered radiation should be ascertained as a function of the angle of emergence for each tube voltage and phantom thickness. PAYNE SCOTT has made such a

calculation for the case of a parallel incident beam, with four different wavelengths (monochromatic).

This calculation gives a clear picture of the great difficulties to be expected if it is desired to determine the distribution of the scattered radiation with the mixed radiation occurring in practice. For this reason we must refrain from drawing up a formula for the absorption of scattered radiation. We therefore confine ourselves throughout this section to one single radiation quality (90 kV, filter 0.5 mm Al + 0.05 mm Cu, 20 cm thickness of a water phantom, 30 × 30 cm²), of which we know the relative intensity as a function of the angle of incidence due to measurements similar to those of SEEMANN.

We shall first apply these measured results to the nine different grids in Diagram 1 as 3 groups of 3 grids each, whereby grids belonging to the same group have the same lead content. The three grids (a, b and c) with lead content of 0.030 cm³/cm² have the ratios of 6.5, 13 and '∞' (lead sheet); the grids d, e and f have a lead content of 0.050 cm³/cm² and the ratios 8, 16 and '∞', whilst the last three have a lead content of 0.078 cm³/cm² and the ratios 11, 22 and '∞'. Apart from the lead-sheets, the grids are designed according to the formula $h = \sqrt{\frac{P}{\mu}}$ so that each grid gives the optimum transmission for primary rays that can be attained with the given lead content and the coefficient of absorption of the interspacing material. In this case μ has been assigned the value of 0.2 which is a good approximation for the usual organic interspacing if we consider the above-mentioned radiation quality.

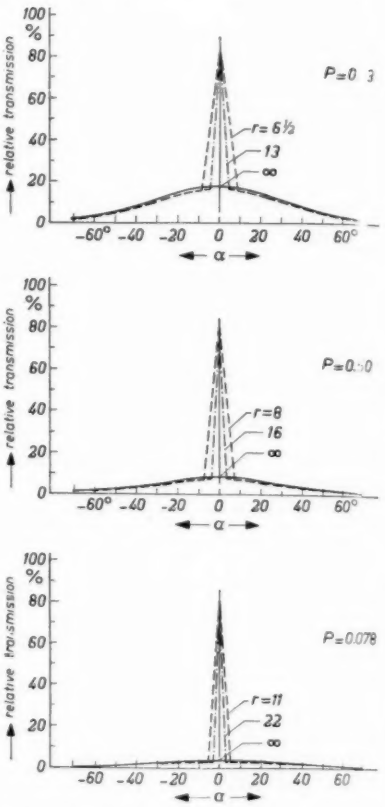

Diagram 2. Relative transmission of scattered radiation as a function of angle of emergence α, for various values of lead contents and various ratios, corresponding to diagram 1: intensity of incident radiation = 100 % in the direction $\alpha = 0$.

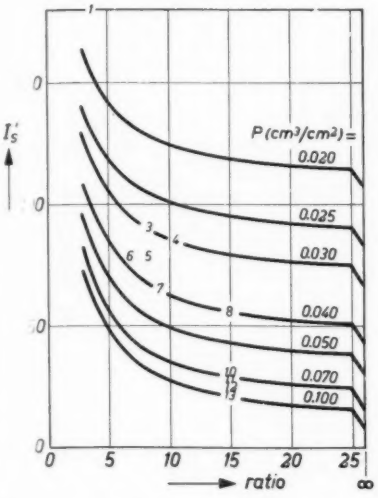

Diagram 3. I'_S = transmitted scattered radiation as a function of the ratio, for various values of lead content P.

In Diagram 2 the relative intensity of the scattered radiation behind these grids is represented as a function of the angle of emergence a, whereby the intensity of the scattered radiation in the direction $a = 0$, before the grids, is taken as 100 % (cf. OOSTERKAMP). The shape of the transmission curve is largely determined by the limiting angle a_l, which can be calculated from $tg\ a_l = \frac{D}{h} = \frac{1}{r}$. This limiting angle decreases with an increasing ratio, and completely vanishes when the ratio reaches '∞' (lead sheet). For angles larger than a_l the absorption is virtually determined only by the lead content, whilst for smaller angles the figures show a peak.

The area under the curves is a measure of the total quantity of scattered radiation transmitted. This area must therefore be as small as possible. This can be attained by making the ratio as large as possible, as a result of which the peak becomes narrow, and by increasing the lead content, as a result of which the rest of the figure is reduced. If the lead content and the ratio are both made very large, the grid will hardly transmit any scattered radiation.

This is clearly shown in Diagram 3, in which the transmission for scattered radiation, Ts, calculated as above, is represented as a function of the ratio for various lead contents between 0.02 and 0.10 cm³/cm². From this figure it appears that when the value of the ratio increases above 10, Ts decreases only slowly. Therefore, whereas in the case of low values the ratio still plays a role, albeit a secondary one compared to the lead content, it can be said that for values of r greater than 10 the quality of a well-constructed grid is almost exclusively determined by its lead content.

In Diagram 3 the grids measured by us are shown in their appropriate places as regards their ratio and lead weight (except for cross-grids 2 and 9). If we consider the location of these points, it becomes clear why we have found that in practice the quality of the grid is judged by its lead content. The differences in Ts between the various grids are indeed far more strongly determined by their lead content than by the difference in ratio.

3. Relation between the ratio and the number of lamellae per cm

By means of the formula $h = \sqrt{\frac{P}{\mu}}$ the relation can now be derived that must exist in a good grid between n and r. Elimination of d and D from (1), (2) and (3) of p. 241 gives:

$$\frac{n}{r} = \frac{1}{h}\left(1 - \frac{P}{h}\right),$$

which means that for a given P and h the ratio is proportional to the number of lines per cm, as is already more or less apparent from Diagram 1.

If the optimum value of $h = \sqrt{\frac{P}{\mu}}$ is used, then the following holds:

$$\frac{n}{r} = (1 - \sqrt{\mu P})\sqrt{\frac{\mu}{P}} = -\mu + \sqrt{\frac{\mu}{P}} \qquad (6)$$

The interpretation of this formula shows that for a given lead content and interspacing and with optimum transmission of the primary radiation, there is a fixed relation between n and r. In this connection the following conclusions may be drawn from formula (6):

1. For a given lead content and interspacing material, a higher number of (thinner) lamellae per cm entails a higher ratio.

2. For a given ratio and interspacing an increase in the number of lamellae per cm can only be obtained at the expense of the lead content, i. e. of the quality.

In Diagram 4, a) and b), the optimum value of h and the corresponding value of $\frac{n}{r}$ are plotted as a function of the lead content, for various attainable values of μ. In this connection it should be noted that for a given interspacing, μ is not a constant, but a function of voltage and of thickness of object.

In order to ascertain how far the measured grids satisfy the conditions of the formulae (5) and (6), we have plotted in the graphs of Diagram 1, a and b, the values of h and $\frac{n}{r}$ of these grids, except for cross grids 2 and 9. It appears that grids 3 to 13 correspond fairly well to the most favourable values attainable. The fact that grid 1 lies so high in the graph for $\frac{n}{r}$ is in conformity with the high μ value (0.5 to 2.0) of its (aluminium) interspacing.

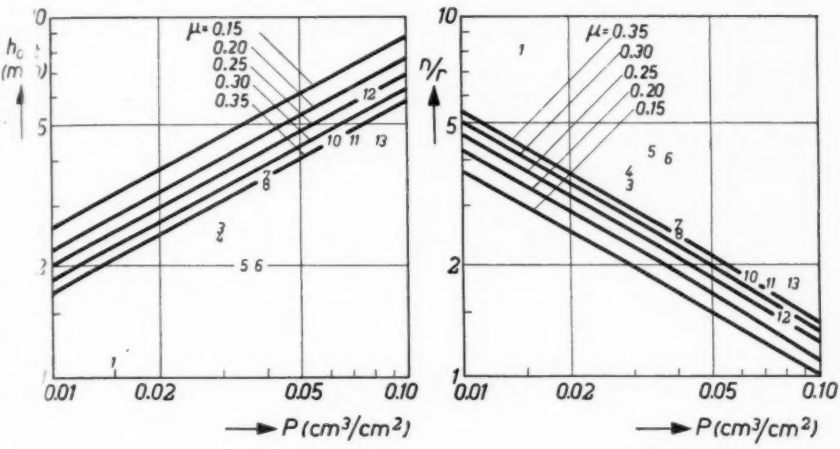

Diagram 4. a) Optimum height h of lamellae. b) $\frac{n}{r} = \frac{\text{number of lamellae per cm}}{\text{ratio}}$ corresponding to optimum height of lamellae as a function of the lead content P and absorption coefficient μ of interspacing material. The numbers correspond to the grids measured.

4. Choice of the ratio

Although it has been shown that the ratio is only of secondary importance to the quality of the grid, it is advisable to choose a ratio as high as is permissible in view of practical limits.

A high ratio is important for three reasons:

I. The peak which is shown by the transmission of scattered radiation for small angles is then small. (This point is negligible for ratios > 10, as explained in section (2).)

II. It is then possible to obtain a greater lead content with a given number of lamellae per cm.

III. By means of a higher ratio more lamellae per cm can be obtained with a given lead content.

Various practical factors, however, militate against the universal application of a grid with a high ratio. In the first place it becomes more and more difficult with increasing ratio to center each lamella so accurately that in the case of correct centering of the focus in relation to the grid all lamellae become correctly directed towards the focus, so that

no undesirable additional absorption of primary radiation occurs; this is detrimental to good contrast and, moreover, sometimes produces an additional shadow.

In the second place, with higher ratios greater losses occur as a result of deviations in the centering of the focus which are inevitable in practice. This factor especially limits the choice of the ratio.

5. Losses due to incorrect centering of the grid

The measured results discussed in part II all refer to stationary and well centered grids at the correct distance from the focus. It is often impossible in practice to satisfy these conditions. Notably as a result of the customary driving mechanisms of the grids and variations in the focal distance, considerable losses of primary radiation occur which are proportional to the ratio of the grid (HONDIUS BOLDINGH).

The graph contained in this publication is reproduced here for the sake of completeness (Diagram 5). This graph may be used in any practical case that may arise to determine the loss occurring at the edges of the image in proportion to the ratio.

The undesired consequences of this loss are: a greater exposure energy (and dose) is required, and loss of contrast occurs at the edges of the film, as appears from the formula $C = C_p \frac{1}{1 + \frac{Is}{Ip}}$.

It may be added that if a grid with parallel lamellae ($fo = \infty$) is used at a focus distance f_1, the loss of primary radiation at a distance c lateral to the focus can be found from the formula $\frac{V}{r} = \frac{c}{f_1}$. This means that the loss now is just as high as when, in the case of a grid with a nominal focus distance $fo = f_1$, the focus is decentered laterally over a distance c.

[7] *The extent of the loss of primary radiation under certain conditions determines the choice of the largest admissible ratio.*

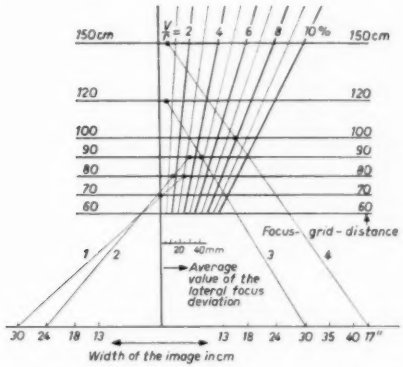

Diagram 5. Graphical determination of the losses of primary radiation due to grid movement, centering deviations, and the use of varying focus—grid distances.

$$\frac{V}{r} = \frac{\text{max. loss of primary radiation at film edge}}{\text{ratio}}$$

6. Choice of the number of lines per cm

If for the given operating conditions (extreme range of focus distances, maximum size of image, average lateral centering error) the largest admissible ratio has been chosen, then it is advisable to use the largest possible lead content. According to formula (6) this means the smallest acceptable number of lamellae per cm. If a driving mechanism is available for the grid, a (normal) small number of lamellae per cm will accordingly be chosen. The lower limit for this number is determined by the condition that the driving mechanism should permit of line-free films with all generally occurring exposure times. If the grid has to be used stationary, a grid with more lamellae per cm must be used. It is a matter of personal choice how inconvenient visible grid lines or groups of lines in the roentgenogram are considered. Grids with about 40 lamellae per cm (100 per inch) are available, which even in the case of direct (contact) exposures satisfy fairly high requirements in this respect, e. g. No. 4 of the table shown in part II, p. 150.

Yet, it should be remembered that with a certain ratio more lines per cm entails a lower lead content and hence less contrast. Therefore, in the case of the comparatively low definition of the screen photography a stationary grid with few lines per cm is to be preferred.

7. Choice of lead content

When the maximum admissible ratio and the minimum acceptable number of lines per cm have been determined in accordance with the above reasoning, a grid is chosen from among the available types of grids (quite apart from preferences for a specific make because of its general quality).

If the grid is always used at a fixed focus distance, if the lateral centering of the grid remains within reasonable limits, and if there is sufficient voltage available, the grid with the largest lead content may be chosen. In all other cases a grid with lower lead content will have to be chosen.

In addition to the fact that according to the foregoing it will often be necessary to restrict the lead content in view of the ratio and the number of lines per cm, it should be remembered that the highest voltage of the available equipment plays a role in the selection of the lead content. It appears from the graphs in Diagram 3, P. II, that the quality standard for a grid is independent of the voltage: a grid which at a lower voltage is superior to another, remains so at a higher voltage.

There is therefore no sense in using a grid with a lower lead content in the low voltage range than in the high voltage range; also in the low voltage range the lead content may be chosen according to the above-mentioned indications.

It is a remarkable fact that the maximum attainable voltage of the available apparatus can set a limit to the lead content chosen. Although at this maximum attainable voltage the best contrast can be obtained with the heaviest available grid, yet there may be cases, notably with small power generators, where it is impossible to obtain the short exposure times required under these circumstances: (still) shorter exposure times can then be obtained by choosing a lighter grid, at the sacrifice of contrast.

This corresponds to the generally accepted view that, for an apparatus with limited voltage and power, a low-ratio grid must be used (which has, as a rule, a low lead content). The argument developed above implies, however, that with an apparatus of this kind, a heavier grid (better contrast) may also be advantageously used side by side with the lighter grid, namely for all exposures giving a sufficiently short exposure time with this grid (Diagram 6).

If interchangeable grids are available, the grid with the lower lead content need therefore only be used for the highest voltages.

From the above remarks it follows that the frequently used term 'high voltage grid' ('Hartstrahlblende') should be avoided, since it

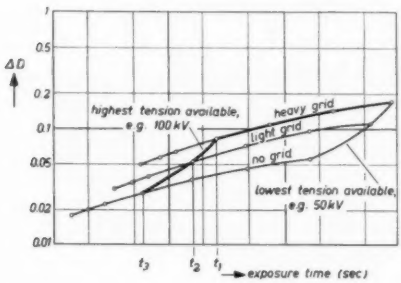

Diagram 6. Choice of a Bucky grid in connection with the power of the available roentgen apparatus:

t_1 shortest exposure time obtainable for a certain case at the highest available voltage, with the heaviest available grid; for lower voltages this grid is to be preferred.

t_2 ditto for the lightest available grid; this grid should be used only for exposure times between t_1 and t_2.

t_3 ditto without grid.

No grid should be used in cases where exposure times between t_3 and t_2 are required.

suggests that these grids are only suitable for use at a high voltage. This is not the case. When under certain conditions these grids, which usually have a high ratio, may be used at a high voltage, they may, in view of their higher lead content, also be used with advantage in the lower voltage range under these same conditions, provided the Bucky factor and, if necessary, the higher dose are compensated by an appropriate increase in voltage.

From the foregoing it will have become clear that great value is to be attached to the lead content in the choice of the grid. Even if the measurements described in this article lead to a greater discrimination between the various types of grid than need be observed in practice, the laws found will still provide an efficient guide in the choice of Bucky grids for different fields of application and working conditions.

8. Comparison with clinical experience

A verification of the heretofore mentioned conclusions on the discussed phantom measurements by means of medical radiographs is not easy for the following reasons:

1. It is difficult, when comparing various grids, to make several exposures of one and the same subject with exactly the same density and exposure time (at different voltages) without many test exposures. Moreover, measurements of this kind should be repeated at various voltages. All this leads to inadmissible radiation doses.

2. It is difficult, if not impossible, with the aid of a few medical subjects which, moreover, consist of a specific combination of tissue and bone structure, to draw more or less general conclusions by means of a subjective judgement of slight variations in contrast.

This must be the reason why some of the 'laws' which have been presented in these articles have not found clear expression up till now in medical practice; moreover, in addition to the difficulties mentioned above there are a few other causes why this has not been the case, namely:

3. We have extended our measurements up to grids of very high lead content, which are not commonly in use.

4. Our measurements have been restricted to small contrasts in one single point of the density curve of the film, $D = 1.0$, with a well defined and constant gradation, whereas in medical practice one has to deal with weak and strong contrasts in small and large density surroundings and therefore with various gradations, which prohibits the drawing of systematic and quantitative conclusions.

However, this does not imply that phantom measurements should be far removed from medical practice; on the contrary, they are so exact and systematic as to enable us to trace quantitative relations and laws which escape observation in practice, but which are nevertheless of importance for drawing up efficient rules for practical use.

The fact that discrimination is less in practice than with phantom measurements means, however, that the tolerance of choice is rather wide, so that in this respect there is no need to aim at perfection. As a result, the number of types of grid applicable to all possible conditions can be limited.

9. Specification data of the grid

The reader will not be surprised that, in conclusion, the authors wish to insist on the desirability of indicating the lead content on each grid as a general rule. Apart from any reference to the manufactured quality and external dimensions it will then be possible to characterize the grid efficiently by means of the following practical and important data:

nominal focus distance
number of lamellae per cm
ratio (in the case of cross-grids 2 × . . .)
lead content, mg/cm²

SUMMARY

The absorption of primary and scattered radiation and the relation between the number of lines per cm, ratio and lead content of grids under optimal conditions is calculated and discussed. Rules are thereby arrived at for a suitable choice of grid for a given field of application. The indication of the lead content (mg/cm²) on each grid is strongly recommended.

ZUSAMMENFASSUNG

Die Absorption der Primärstrahlung und der Streustrahlung und die Beziehungen zwischen der Anzahl der Linien per Zentimeter, der Ratio sowie dem Bleigehalt von Gittern unter bestimmten Bedingungen wird berechnet und diskutiert. Regeln werden aufgestellt für geeignete Gitterwahl für eine gewisse Feldapplikation. Die Angabe des Bleigehaltes (mg/cm²) in jedem Gitter wird sehr empfohlen.

RÉSUMÉ

Les auteurs étudient et calculent l'absorption du rayonnement primaire et du rayonnement diffusé et les relations entre le nombre de lamelles par centimètre, le rapport de grille et la teneur en plomb dans les conditions optimum. Ils en déduisent des règles pour le choix d'une grille convenant à un domaine d'utilisation donné. Ils recommandent vivement que soit indiqué sur chaque grille sa teneur en plomb (mg/cm²).

REFERENCES

(For list of references, see part I, Acta Radiol. 51 (1959), 489.)

BOOK REVIEWS

DOSE DISTRIBUTIONS IN ARC THERAPY IN THE 200 TO 250 kV RANGE. Systematic measurements in homogeneous phantoms with the beam direction perpendicular to the oscillation axis. Text in English and German. By Olov Dahl and Karl Johan Vikterlöf. 250 pages, 157 isodose charts, 21 illustrations and 8 tables. Acta radiol. Suppl. 171 (1958). Sw. Kr. 35: —.

Numerous variations of technique are employed in moving beam therapy. As we found that the nomenclature used in all such techniques was not uniform and consistent we considered it necessary to devise our own terminology; this is presented in an introductory section.

One important task in all roentgen therapy must be to settle the different variables in the treatment conditions in such a way as to ensure the clinically optimal dose distribution. This often requires a series of standard isodose charts for the method in question.

It is evident from the literature that, so far as perpendicular axial arc therapy in the 200 to 250 kV range is concerned, a large number of very useful measurements of dose distributions in the oscillation plane have been reported. It was not found possible, however, to arrive at any generally utilizable series of isodose charts from the results published.

For the purpose of producing diagrams which would prove serviceable under defined circumstances as standard isodose charts for perpendicular axial arc therapy, a number of dose distributions in the oscillation plane were measured and arranged in different series. In accordance with the general practice in roentgen therapy the measurements were primarily carried out in homogeneous phantoms, various models, mainly cylindrical in shape, being used in the series.

The apparatus consisted of a Siemens-Reiniger-Werke arc therapy unit fitted with an oil-immersed SRW 220/20 roentgen tube and operated at a constant potential of 200 kV. Added filtration of 0.5 mm Cu + 1 mm Al corresponded to a radiation quality of HVL 1.1 mm Cu. We showed, however, that the isodose charts, except for the dose rate factors given, would be largely valid for corresponding arc therapy with radiation qualities within the range from HVL 0.7 mm Cu to HVL 2.0 mm Cu. The charts are also valid on the whole for nominal focus—surface distances between 40 and 60 cm and nominal surface field lengths above 5 cm.

The measuring equipment consisted of twenty uniformly designed condenser chambers of Sievert's type together with a Philips universal dosemeter. These microchambers, only 20 mm in length and not more than 5 mm in diameter, were subjected to extensive control tests for roentgen constants, energy dependence, dose linearity and direction dependence and proved to meet the requirements for radiation detectors suitable in comprehensive dose distribution studies.

The principal variables in the treatment conditions were assumed to be the oscillation angle, the centering depth (*c*), the width (*a*) and the length (*b*) of the nominal surface field. The intervals chosen for each variable were 40° (60°, 100°, etc), 2.5 cm (0, 5, etc), 1.0 cm (2.0, 3.0, etc) and 3.0 cm (5.0, 8.0, etc), respectively.

The dose distributions were investigated in two planes through the nominal entrance point perpendicular to each other, namely, the oscillation plane and the plane of symmetry. In the oscillation plane we measured 402 distributions in seven different models, using different combinations of oscillation angle, *c*, and *a*. In the plane of symmetry, on the other hand, we considered that the main clinical interest was to establish the influence on the extension parallel with the oscillation axis of the isodose contours with the highest relative dose values. In so doing, it was found that a correlation between the nominal surface field length (*b*) and the extension parallel with the oscillation axis of *e. g.* the 75 or 90 per cent isodose contours could be represented diagrammatically by a straight line. In fact, this relation may be employed with satisfactory accuracy for practical use in combination with any of the isodose charts in the oscillation plane presented, and so give an idea of the corresponding three-dimensional dose distributions.

The great majority of the measurements were made with the model positioned symmetrically in relation to both the oscillation plane and the plane of symmetry of the oscillation and with its axis parallel to the oscillation axis. To investigate the influence upon the dose distribution of asymmetry of the phantom in relation to the plane of symmetry of the oscillation we also made a series of measurements using an asymmetry of 5 and 10 cm.

The selection of charts for publication was based, as far as possible, on the considerations arising in the treatment of tumours of varying size and at varying depths in different parts of the human body. The charts selected from each phantom were arranged with respect to the approximate depth of the dose maximum and to the approximate size of the area within the 90 per cent isodose contour, this arrangement implying progressively larger and deeper 90 per cent isodose areas.

Some charts were selected chiefly for the purpose of illustrating the influence of the phantom dimensions and each of the variables, oscillation angle, *c* and *a*, upon the dose distribution in the oscillation plane, this circumstance being briefly discussed in a concluding section.

Autoreview

La Méniscographie en Série du Genou. Par S. De Sèze, A. Djian, R. Calop, et H. Puchot. Numéro spécial des 'Monographies Médicales et Scientifiques' Janvier 1958 — No. 8 Monofilms. 63 pages, 73 figures. Edit. Garnier, Paris 1958. Fr. 900: —

After a survey of the normal anatomy of the knee joint, the technique of arthrography and the appearances of normal and ruptured menisci are described and illustrated. Gas alone or in combination with a small amount of contrast medium is used for the demonstration of the menisci. Traction is applied in order to keep the menisci away from the condyles though, as usual, not always very successfully as far as the posterior half of the medial meniscus is concerned.

Some comparison between the results obtained with different methods of arthrography as well as an account of the accuracy of the arthrographic diagnosis are really required before the value of the author's work can be assessed.

K. Lindblom

NORMALE UND PATHOLOGISCHE ENTWICKLUNG DES MENSCHLICHEN HERZENS. Von Klaus Goerttler. 123 S., 54 Abb. Georg Thieme Verlag, Stuttgart 1958. DM 33.

This book which constitutes Volume 3 in the series Zwanglose Abhandlungen aus dem Gebiet der normalen und pathologischen Anatomie, edited by W. Bargmann and W. Doerr, describes the development of the normal and malformed heart, and of those parts of the circulatory system directly connected with it.

The author's presentation of the relevant problems is unconventional and differs in many respects from current conceptions. The fundamental anatomic features of the development of the cardia septa and of the infundibulum of the right ventricle are, for example, only briefly described. As a comprehensive introduction to a description of many of the common congenital cardiac malformations which are amenable to surgical correction, these matters are generally dealt with in other publications in great detail. The author on the other hand has taken as his main task an elucidation of those factors which affect the normal and pathologic development of the heart. He bases his descriptions upon investigations on the circulatory conditions performed in glass models of the embryonic heart primordium, upon the distribution of mitoses in serial sections of the embryonic chick heart, and upon conclusions drawn from studies of specimens of malformed hearts. The embryonic heart must be seen as an entity; the development of the septa is a secondary phenomenon, which depends on the elongation and bending of the heart tube, which grows asymmetrically. The true cause of a cardiac malformation is a developmental arrest, produced by endogenous or exogenous factors, of segments of the myocardium which, at different stages, are particularly active metabolically. The anatomy is influenced secondarily by the altered dynamics. Goerttler's book gives a most vivid picture of the interplay between these factors. The extent to which the author's views, some of which are presented as working hypotheses, are sufficiently sound to permit of new conceptions of certain important aspects of the embryology of the heart can presumably be judged only by those with extensive knowledge in this field.

For the roentgenologist engaged in practical work and with an interest in cardiologic problems, the chief merit of the book is that it gives a valuable insight into the complicated mechanisms underlying anomalies of the heart. The drawback that part of the terminology is difficult to understand is to some extent offset by the excellent illustrations.

Ulf Rudhe

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY. Published by Taylor & Francis. London. Editor: Dr. W. M. Dale, Department of Biochemistry, Christie Hospital, Manchester 20.

The first issue of a new scientific journal, founded to publish original papers "in radiation biology and related studies in physics, chemistry and medicine" has appeared. The international character of the project is evidenced by the list of members of the Editorial Board, representing some 15 countries, as well as by the fact that articles will be accepted in English, French, or German. The first number contains papers within the following fields: the mechanism of radiation protection, radiation effects on the synthesis of deoxyribonucleic acid, radiation chemistry, and effects on enzymes, as well as genetic problems. Surveys of two recent international meetings, namely the International Congress in Radiation Research in Burlington and the European conference on the Use of Ionizing Radiations for Food Preservation are also included.

It may be expected of this new periodical that it will fill a vacancy among publications devoted to the ever increasing amount of scientific work in these fields.

Arne Forssberg